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Cleveland Clinic Quarterly

TREATMENT OF UREMIA

Use and Indications for High Caloric Low Protein Diet, Dialyzing Methods and Replacement Transfusion

W. J. KOLFF, M.D.
Research Division

IN the presence of acute anuric uremia and in chronic uremia, regardless of the cause, several principles should guide treatment. These are: 1. maintenance of body fluid and a certain electrolyte balance, 2. maximal suppression of protein metabolism, 3. avoidance of infection and 4. elimination of retention products ordinarily removed by the kidneys.

1. Control of Fluids and Electrolytes

Unfortunately many patients with oliguria and acute uremia are overtreated with water and saline in the hope that diuresis will occur, but no amount of fluid will induce urine formation if the uremia is due to parenchymal renal disease. Conversely, if given to patients in whom urine formation does not occur, salt and water will lead to the development of edema greatly endangering the ultimate prognosis. To avoid such unnecessary complications during periods of urinary suppression the daily intake of fluid should be rigidly limited to 750 cc., while fluid lost with vomiting and diarrhea may be counterbalanced.

Correct control of electrolytes can be accomplished only if their concentration in the blood and body fluids is known, hence frequent measurements of CO_2 combining power, sodium chloride and potassium levels in the blood plasma are part of the management of acute uremia. Moderate depression of sodium chloride may be an advantage since it reduces the blood pressure, and diminishes the risk of convulsions and congestive heart failure. Vomiting and diarrhea however can cause excessive sodium and chloride loss. Such states will further depress urine formation and lead to more severe azotemia.

Careful replacement of these ions orally, if possible, or by intravenous administration of 3 or 5 per cent sodium chloride may be indicated.

Acidosis can be, in part, controlled by a high caloric intake. However, should CO_2 combining power fall below 25 volumes per cent, sodium bicarbonate may be given orally or intravenously. Six to 10 Gm. per day should rarely be exceeded.

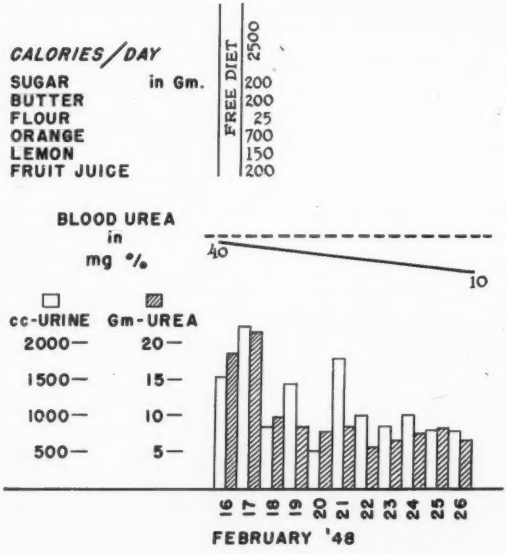
Potassium deficiency is not uncommon in chronic uremia but it is relatively rare in acute anuric uremia where hyperpotassemia is a frequent cause of death.[8] Hyperpotassemia may be corrected by the oral administration of exchange resins (potassium free amberlite) which fixes potassium in the bowel, by the forced feeding of large amounts of carbohydrates or by one of the dialyzing procedures[8] to be mentioned later.

Should calcium levels become low enough to cause tetany or nocturnal cramps, replacement by means of calcium gluconate or chloride is indicated.

It is said that hyperphosphatemia can be corrected toward normal by aluminum hydroxide given by mouth. This drug precipitates phosphates in the bowel so that they are eliminated in the stool. I have had no personal experience with this method.

2. Supression of Protein Metabolism

Suppression of protein metabolism by high caloric, protein-free feedings has been shown favorably to influence uremia in laboratory animals (Masson, Corcoran and Page[10]). The protein-sparing effect of a high caloric diet was shown distinctively by Borst;[2] the essentially new point in his treatment is the forced consumption of quantities of carbohydrate and fat adequate to cover the patient's caloric needs. If caloric intake is high enough, urea excretion may be reduced to as little as 2 to 5 Gm. per 24 hours. Graph 1 follows the course of a healthy student who was given 2500 calories but a minimal amount of proteins. Within 5 days his urea excretion (and production) was reduced to 5 Gm. per day. Should this man have become completely anuric with continuation of the diet he would have lived 25 days before his blood urea would



GRAPH 1. Normal student with healthy kidneys on forced high caloric nonprotein diet. His daily urea excretion is reduced from 22 to 5 Gm. per 24 hours on 2500 calories per day. The blood urea having been only 18 mg. per hundred ml. urea production could not have been much more than 5 Gm. per day.

have reached a level of 350 mg. per hundred ml. Moreover, excessive accumulation of urea and other products of protein catabolism can be avoided in patients with minimal renal function.

Patients with uremia usually are nauseated and, unless much care is used in preparation, the diet may not be ingested in adequate amounts. With persuasion and explanation of the importance of dietary measures, most patients will undertake the effort. When a sense of well-being is experienced—they become cooperative and manage in some way to consume 2000 calories per day. The mixture of butter and sugar, suggested by Borst, is probably most effective for a sick patient. As improvement occurs the diet can be expanded to include 20 Gm. of protein per day plus the amount lost in the urine, with generous quantities of carbohydrate and fat. Kempner and others have shown that 20 Gm. of protein will (or almost will) maintain patients in nitrogen balance for several years, but only as long as caloric intake is adequate.

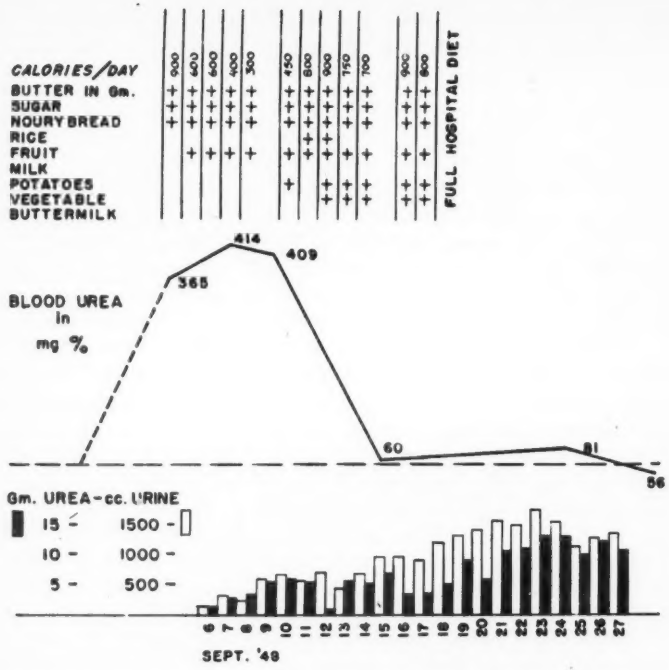
During acute uremia some patients are unable to ingest or retain the butter and sugar mixture. For these patients adequate calories can be provided by dripping an emulsion of peanut oil and glucose (Bull, Joekes and Lowe[3]), or LipoMul-Oral* through a nasal tube leading into the stomach or small intestine. In critical cases with intractable vomiting or diarrhea, even this method may fail. In such desperate cases we have resorted to a slow continuous drip of 40 per cent glucose through a small plastic cardiac catheter in the right auricle. One liter per 24 hours furnishes 1600 calories. Thus fluid intake is kept low and thrombophlebitis caused by hypertonic glucose is avoided. Heparin, ±150 mg., per 24 hours mixed with the infusion will prevent clot formation on the outside of the catheter, while antibacterial drugs discourage infection. Observing these precautions, catheters have been left in place 20 days without undesirable results. At the conclusion of this article Marjorie Curry and June E. Thompson describe Borst's and Bull's mixture and the preparation of various high caloric low protein diets.

Graph 2 shows the course of a 6-year-old girl, anuric for probably 14 days, who was forced to take the high caloric diet. It should be noted how rapidly the blood urea fell with the recovery of kidney function even when only 5 to 6 Gm. of urea was excreted per 24 hours.

3. Avoidance of Infection

People with uremia are liable to infection which promotes protein breakdown and increases the uremia. For prevention and treatment of such complications, antibacterial drugs should be used. Because of depressed renal function sulfonamides are to be avoided and for the same reason penicillin and aureomycin may be given in smaller amounts at less frequent intervals.

**A fat emulsion for oral nutrition developed by Shoshkes, Van Itallie, Geyer and Stare (J. Am. Dietet. A., Volume 27, March 1951) and manufactured by the Upjohn Company under the trade name of LipoMul-Oral seems to provide the most satisfactory solution to the problem. We have only recently utilized this emulsion.*



GRAPH 2. Six-year-old girl with acute glomerular nephritis; probably anuric for approximately 14 days. While forced to take 900 or 600 calories a day the blood urea rose from 365 to 414; it then began to fall notwithstanding small urea output. Note increase of urea excretion when patient was allowed full hospital diet.

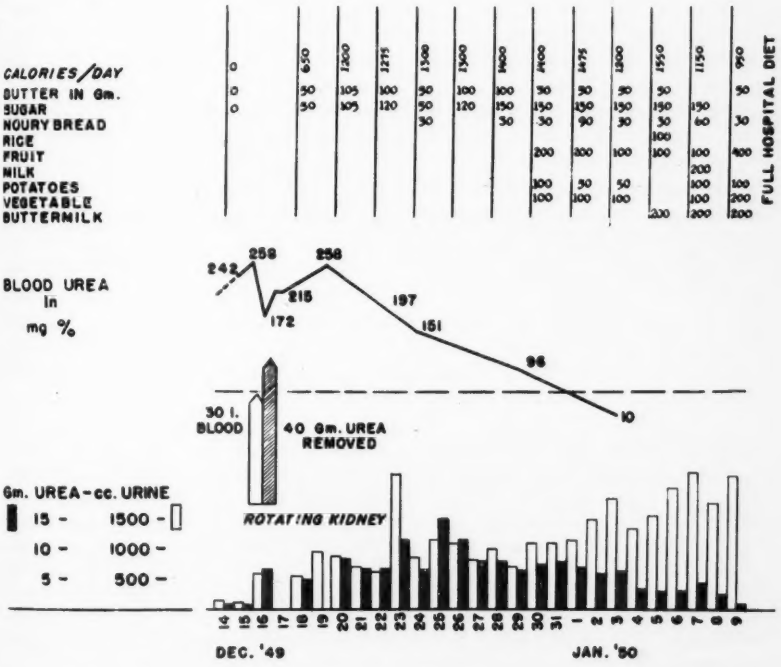
4. Elimination of Retention Products

A. Artificial Kidney. If the measures recorded previously are applied vigorously at the onset, most patients with acute anuria resulting from recoverable lesions will diurese before dialyzing methods are necessary. However, if such measures have not been observed, or if burns, crushing injuries or infection have caused excessive protein breakdown, treatment by some form of dialysis may be necessary. One of these is the artificial kidney described in the October 1950 *Cleveland Clinic Quarterly*.[6,7] Use of the artificial kidney presents little danger in experienced hands and, in patients seriously ill with acute anuria, a single treatment may restore well-being to the extent that dietary measures may be applied.

An illustrative case is shown in graph 3. This 49-year-old woman gave a vague history of acute glomerulonephritis. She was anuric and suffered from congestive heart failure and pulmonary edema made worse, if not precipitated, by excessive treatment with saline solution. Because of her ominous state she was immediately treated with

the artificial kidney. Thereafter she was able to ingest a high caloric diet in increasing amounts and made a satisfactory recovery.

Although the artificial kidney is most useful in acute uremia due to renal lesions from which one may recover, it occasionally is applicable in instances of chronic uremia due to glomerulonephritis or polycystic kidney disease. Among this group of patients acute exacerbations of nephritis, infections, nausea and vomiting and associated symptoms may impel a patient with compensated renal insufficiency into terminal uremia. The artificial kidney is often extremely valuable in such periods of crisis. Some patients who are ill with uremia and an unknown primary disease can be kept alive by this form of dialysis until a definite diagnosis is established. In short the artificial kidney may be applied in any case of uremia where life is in jeopardy, and where the uremia is thought to be the cause of the immediate danger.



GRAPH 3. Forty-nine-year-old woman with acute glomerular nephritis, congestive heart failure and pulmonary edema. In single treatment with artificial kidney 40 Gm. of urea was removed and signs of pulmonary edema disappeared when fluid was withdrawn by hypertonic glucose solution in rinsing bath of the artificial kidney. One day after treatment patient was able to take 650 calories and shortly thereafter the diet was extended. Note low urea output (3 Gm.) on January 4, 5 and 6 while blood urea was low, demonstrating low urea production.

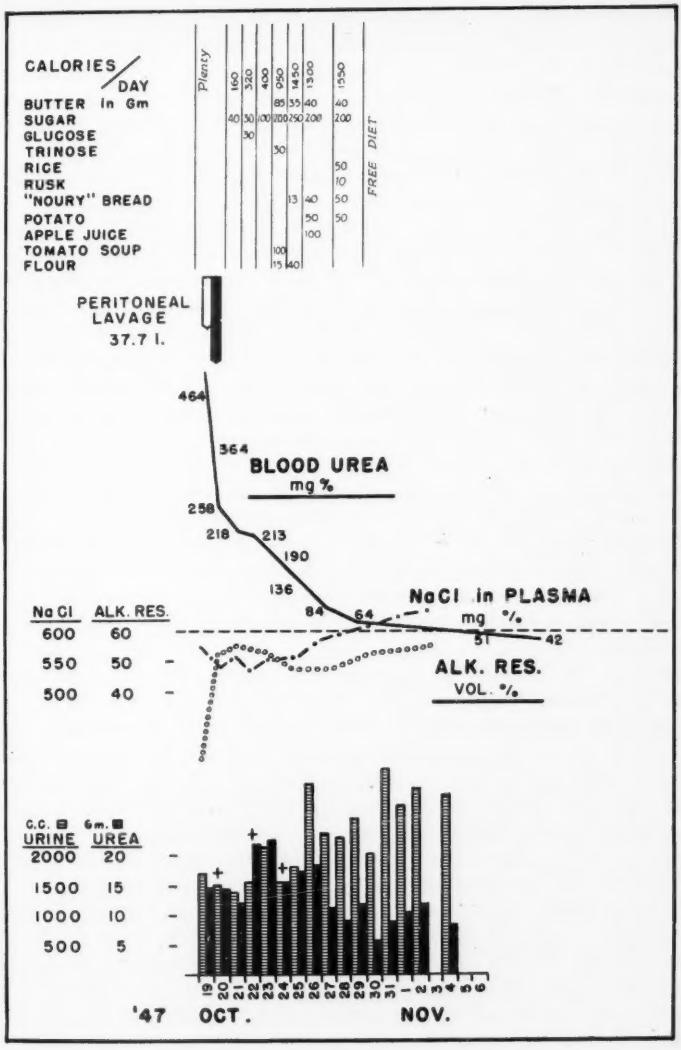
The artificial kidney will: (1) remove retention products (it is now well established that such treatment will prolong the lives of patients having anuria, and of nephrectomized animals); (2) correct electrolyte imbalance; (3) relieve edema, particularly pulmonary edema, and (4) furnish large amounts of glucose by dialysis which, while not essential, may be useful.

B. Peritoneal Lavage. Frank, Seligman and Fine[4] revived peritoneal lavage as a treatment for uremia in 1946. Until 1948 there were 34 reported patients treated in this manner, of which 9 recovered. However, there were many failures due to maladjustment of the composition of the rinsing fluid and to peritonitis. In 1948 Kop[9] reviewed his own and Kolff's[7] experiences with peritoneal dialysis performed 35 times on 21 patients; 7 of these patients recovered. Nine who had chronic glomerulonephritis or malignant hypertension died. However, even in this group there was temporary subjective and objective improvement. The method has been tried in many centers and generally abandoned (1) because of mechanical difficulties which sometimes prevent adequate drainage of the peritoneum, (2) because of the difficulties encountered in controlling water and electrolyte balance in such cases, and (3) because of the development of fatal peritonitis. The latter complication is explained by the work of Schweinburg, Seligman and Fine[12] who demonstrated that radioactive B. coli could pass through the intestine into the peritoneum. In our group, peritonitis was not a problem, possibly because dialysis never lasted longer than 72 hours and usually no more than 24 hours. In one day retention products are reduced adequately enough to relieve immediate danger so that dietary measures may be effective.

Our technics have been described elsewhere (Kolff,[7] Kop[9]). Briefly, small rubber or plastic tubes are introduced into the peritoneum through trocars. One is connected to a special tank containing 28 L. of electrolyte containing fluid to be delivered at the rate of 1 L. per hour. Inflow and outflow can be interchanged by changing clamps and without opening tubes. Antibiotics and heparin are added to this rinsing fluid.

A 38-year-old woman (graph 4) developed fever and abdominal pain during the seventh month of pregnancy. She was treated with sulfadiazine but suffered a retroplacental hemorrhage and was delivered of a dead child. In retrospect it was established that oliguria began at this time but the degree and exact duration could not be determined. On the seventh postpartum day, she experienced abdominal cramps and diarrhea and was given sulfaguanidine. On the fifteenth day postpartum she was transferred to our service in a comatose state. Blood pressure was 150/80; breathing was of the Kussmaul type; the blood urea was 464 mg. per hundred cc. Twenty-four hours of peritoneal dialysis removed 57 Gm. of urea and reduced the blood level to 258 mg. per hundred ml. The alkali reserve was restored to normal while the chlorides remained unchanged. Diuresis began during dialysis and recovery was complete.

Indications for peritoneal lavage are the same as those for the artificial kidney. Peritoneal dialysis is a much simpler and less elaborate procedure; however underestimation of the difficulties of the procedure may prove disastrous in inexperienced hands. Some patients find the therapy extremely unpleasant and even painful. Furthermore, one can never be certain about the return flow of peritoneal fluid. This is also true if the method of periodical



GRAPH 4. Thirty-eight-year-old woman. Serious condition relieved within 24 hours with one peritoneal lavage. A high caloric diet was prescribed but as the kidneys had obviously opened up and her abdomen was painful after the peritoneal lavage, it was not emphasized. (Noury bread is a low protein bread made in Holland by Nourypharma Deventer.)

installation and withdrawal is used as recently advocated by Grollman and others.[5] If the outflow is inadequate, patients can become dangerously overloaded with electrolytes and water. In the presence of ascites it is usually simple to dialyze through the peritoneum while, if the intestine is distended, the procedure is difficult. If patients are overhydrated or there is evidence of pulmonary edema, the artificial kidney is a much safer process; if the patient is dehydrated lavage may help to correct it. In patients who have recently been operated upon, or who have infection or skin lesions, peritoneal dialysis should be avoided.

Merrill and his associates have given heparin to a patient with a peptic ulcer shortly after a gastric hemorrhage and have treated him with the artificial kidney without consequent harm, and we have observed the cessation of epistaxis during this treatment; however, if bleeding tendencies exist, peritoneal dialysis generally takes precedence over the artificial kidney.

C. Intestinal Dialysis. It has been established that lavage of the colon and stomach are of no value for the removal of retained urinary products. E. E. Twiss has recently published (1950) a monograph of the work done with this method in Kolff's Clinic in Kampen, Holland.[13]

Large amounts of urea and other retention products can be removed by intestinal dialysis and there is no doubt that uremia can be relieved sufficiently by this method. Using a cellophane membrane or a peritoneal membrane (as described previously), there is no cellular activity in the membrane and it is not difficult to balance the electrolytes on both sides of the membrane. In using the intestinal mucosa, however, absorption takes place, which must be compensated by the osmotic pressure and the particular composition of the rinsing fluid.

Apart from accepting the principle that neither strongly hypertonic nor hypotonic solutions should be used to avoid damage to the intestinal epithelium, we could draw the following conclusions from the dog experiments:

1. To prevent fluid absorption the solutions must be made moderately hypertonic. This can be done by adding sucrose (with or without glucose) or glucose-ureide, by adding magnesium or sodium sulfate, or a combination of these substances to the solution. If sugars are added to the solution its osmotic activity should be higher than when sulfates are added, as these salts are absorbed more slowly than the sugars.

2. If the solution contains sodium: 24 mEq/L, bicarbonate 24 mEq/L, potassium 5 to 6 mEq/L, calcium 5 mEq/L and chloride 10 mEq/L* electrolyte equilibrium usually exists between the intestinal lumen and the blood, with an occasional slight chloride loss. The bicarbonate ion possibly is exchanged partly for the chloride ion, indicated by the lowering of the pH of the solution; this will contribute to the correction of uremic acidosis in patients.

No more than 100 mg. per hundred ml. of sodium chloride should be added to the solution, unless absorption of sodium chloride is desired. Any loss of sodium chloride during intestinal perfusion can be restored easily.

**These concentrations are obtained by adding to the solution per 100 ml.: sodium bicarbonate 200 mg., potassium chloride 40 mg. and calcium chloride (the pure salt) 28 mg.*

3. The addition of sucrose, with or without glucose, to the solution is advantageous in that a considerable part of the sugars will be absorbed (as hexoses) and increase the caloric intake of the uremic patient.

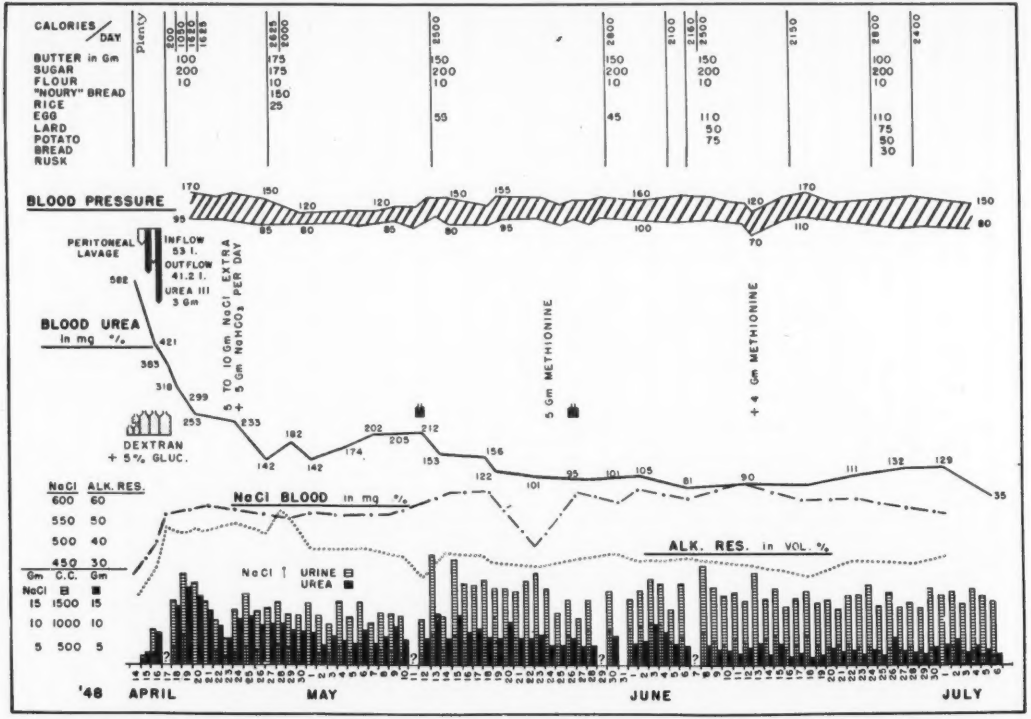
4. Magnesium and sodium sulfate have proved suitable for maintaining the osmotic activity of the perfusion fluid. Some magnesium and probably more sodium are absorbed; this is disadvantageous in that hypermagnesemia may occur (especially in anuria) with the danger of depression of respiration, and because too great an absorption of sodium from the sodium sulfate-containing solutions may aggravate the disturbance of homeostasis of the body fluids and lead to serious hypertensive crises.

The following is an example of the composition of such a rinsing fluid: NaCl O, $NaHCO_3$ 200, KCl 40, $CaCl_2$ 28, sucrose 6000, glucose 3600 mg. per hundred ml. The osmotic activity is 484 m. osmols/L. However, as Visscher has already indicated, the cells of the intestinal mucosa may be changed; for example: by perfusion with aqua destillata or by the addition of a trace of bichloride of mercury. At present it is extremely difficult or impossible to predict how the mucosa of a certain patient is liable to react and, if an intestinal dialysis is done, constant supervision of the blood plasma electrolytes is necessary.

Two methods of intestinal dialysis have been used. (1) Intestinal dialysis using the entire tract for the treatment of acute uremia. (2) Dialysis through an isolated intestinal loop for the treatment of chronic uremia. In (1) the fluid is introduced through a jejunal tube at a rate of 1 L. per hour and the outflow is affected through a large tube in the rectum.

The intestinal peristalsis moves the rinsing fluid from the oral to the distal parts of the intestines. However, I have seen paralysis occur, making it virtually impossible to recover any of the introduced rinsing fluid. After having witnessed the treatment of a dozen patients by a man as experienced as Dr. Twiss, I am still unconvinced that intestinal dialysis, using the entire tract, has an advantage over the artificial kidney or peritoneal lavage.

(2) Since the first uremic patient was treated, in 1946, with dialysis through an intestinal loop, we have been alert for patients in whom the uremia was severe enough and the condition distressing enough to justify a trial with this form of dialysis. About 2 meters of small intestine are used, the ends of which are sutured in the abdominal wall simulating an artificial anus; the remainder of the gut is anastomosed end to end. While the remaining intestinal tract will accommodate the patient's digestive function, the isolated loop may be used for dialysis. It is not difficult to prove that from 5 to 10 Gm. or even more of urea can be removed by dialysis through such an intestinal loop in the course of 8 to 10 hours; this amount of urea is sufficient as long as the patient is maintained on a high caloric low protein diet. The ultimate incentive is to dialyze the patient nocturnally during sleep and to have him perform his customary work in the daytime. One man who was virtually nephrectomized was maintained on this regimen for 46 days. He has been in urea balance for 16 consecutive days by utilization of the intestinal loop. (He died from a cerebral vascular accident.) Inasmuch as most patients with chronic uremia do well on



GRAPH 5. Forty-nine-year-old man with polycystic kidneys and hypertension admitted with blood urea of 580 mg. per hundred ml. After peritoneal lavage lasting 2 days, he was able to take butter and sugar diet. When caloric intake was covered, 5 Gm. of methionin, 2 eggs, and 50 Gm. of ordinary bread were allowed without noticeable increase in urea excretion. Blood urea varied between 130 and 35 mg. per hundred ml.

the forced high caloric diet as described before, we have had few opportunities to repeat this procedure.

D. Exsanguino or Replacement Transfusion. Exsanguino transfusion has been introduced by Bessis[1] in the treatment of uremia. In this method a large volume of blood is infused in one arm while an equal volume is removed and discarded from the other arm. It is easy to calculate how much blood should be withdrawn to remove a certain amount of urea. If the blood urea is 400 mg. per cent the removal of 1 L. of blood will eliminate almost 4 Gm. of urea. The removal and replacement of 5 to 7 L. of blood every other day would be an expensive procedure in this country. Even when utilizing this process the amount of retention products which can be removed is less than when using dialyzing methods. I have used this form of treatment in many cases of uremia to restore the hemoglobin. If a patient with uremia is transfused in the ordinary way there is definite danger that he will develop congestive heart failure and pulmonary edema. It is more satisfactory to remove an equal, or preferably larger, volume of blood from the patient at the same time. If fresh, concentrated red cells are transfused instead of whole blood, this method is even more effective. One patient had a blood urea of 242 mg. per cent. Nine bottles of blood were removed, and at the same time 8 bottles of blood were reinfused. Immediately following this procedure the blood urea was found to be 233. The hemoglobin content, however, was restored without evidence of having overburdened the circulation.

The smallest scale in which this procedure may be used is the withdrawal of 500 ml. of the patient's blood in a transfusion bottle. After sedimentation, which takes place in 1 hour, the plasma should be discarded and the red cells reinfused. This may be done when a venesection is necessary in severely anemic patients.

E. Cross or Exchange Transfusion. During this procedure equal amounts of blood are transfused from a healthy donor to the patient and from the patient to the healthy donor. Cross transfusion has been practiced successfully in dogs for a long time. It is possible to reduce the blood urea of a uremic dog to about half its previous level by means of cross transfusion within a few hours. After extensive studies[11] this method was applied to human beings by Salisbury. Unfortunately a phenomenon occurred never observed in hundreds of experiments on dogs. A healthy donor, cross transfused with a patient having nephrosis, failed to recover. He developed an incurable blood disease, perhaps best described as a panmyelophthisis, and died 20 days after the cross transfusion. Once this has been observed further clinical cross transfusion is out of the question.

In conclusion graph 5 outlines the course of a patient with severe chronic uremia in whom many of the previously described procedures have been applied.

A 49-year-old man who had polycystic kidneys and hypertension for many years was admitted in poor condition with a blood urea of 582 mg. per cent. He was dehydrated, acidotic and had hypochloremia. Peritoneal lavage removed 111 Gm. of urea. His shock was treated with intravenous infusion of Dextran (Makrodex) and his alkali reserve and serum chlorides were corrected.

was covered, 5 Gm. of methionin, 2 eggs, and 50 Gm. of ordinary bread were allowed without noticeable increase in urea excretion. Blood urea varied between 130 and 35 mg. per hundred ml.

Makrodex* is a complex glucose molecule which may be used as a blood substitute. In patients with uremia it has the advantage of being broken down to glucose, which aids the caloric intake, rather than to amino acids and urea like most other substitutes as well as plasma.

Summary

Restriction of water and electrolytes are imperative in the treatment of acute anuric uremia. Clinical judgment and laboratory technics should control water and electrolyte balance if the kidneys are unable to do so, as in the diuretic phase of acute uremia and in many cases of chronic uremia.

The forced high caloric low protein diet (Borst) prolongs life in cases of acute uremia and in addition may make life worth living in chronic uremia. Artificial kidney and peritoneal lavage may help a patient through an acute phase of the disease toward recovery or in chronic cases may restore the patient's nitrogen equilibrium. Intestinal dialysis employing the entire tract appeared difficult and exhausting to patients in severe clinical condition. Dialysis through an isolated loop offers a chance to those patients with chronic uremia to whom we can offer nothing else. Replacement transfusions are useful in the restoration of hemoglobin but cumbersome when utilized to combat uremia. Makrodex is preferred over other blood substitutes if hypotension has to be treated in patients with uremia.

I wish to thank Dr. Robert D. Taylor for his assistance in preparing this manuscript.

References

1. Bessis, M.: Use of replacement transfusion in diseases other than hemolytic disease of newborn. Blood **4**:324 (April) 1949.
2. Borst, J. G. G.: Protein catabolism in uraemia; effects of protein free diet, infections, and blood transfusions. Lancet **1**:824 (May 29) 1948.
3. Bull, G. M., Joekes, A. M. and Lowe, K. G.: Conservative treatment of anuric uraemia. Lancet **2**:229 (Aug. 6) 1949.
4. Frank, H. A., Seligman, A. M. and Fine, J.: Further experiences with peritoneal irrigation for acute renal failure, including description of modifications in method. Ann. Surg. **128**:561 (Sept.) 1948.
5. Grollman, A., Turner, L. B. and McLean, J. A.: Intermittent peritoneal lavage in nephrectomized dogs and its application to human being. Arch. Int. Med. **87**:379 (March) 1951.
6. Kolff, W. J.: Artificial kidney. Cleveland Clin. Quart. **17**:216 (Oct.) 1950.
7. Idem: New Ways of Treating Uraemia, Monograph. London, J. and A. Churchill, Ltd., 1947.
8. Idem: Serum potassium in uremia; report of 16 cases. J. Lab. and Clin. Med. **36**:719 (Nov.) 1950.
9. Kop, P. S. M.: Peritoneal Dialysis, Monograph. Kampen, Holland, J. H. Kok, N. V., 1948.
10. Masson, G., Corcoran, A. C. and Page, I. H.: Dietary and hormonal influences in experimental uremia. J. Lab. and Clin. Med. **34**:925 (July) 1949.

**Makrodex was supplied by Pharmacia in Sweden and by Mr. Nathan Katz, Pharmacia Laboratories, Inc. 2 Park Avenue, New York 16, N. Y.*

11. Salisbury, P. F. and Miller, J. H.: Cross transfusion; therapeutic effect in acute mercury nephrosis. Proc. Soc. Exper. Biol. and Med. **74**:16 (May) 1950.
12. Schweinburg, F. B., Seligman, A. M. and Fine, J.: Transmural migration of intestinal bacteria; a study based on use of radioactive Escherichia coli. New England J. Med. **242**:747 (May 11) 1950.
13. Twiss, E. E.: Treatment of uremia by dialysis and other methods with special regard to the principles and scope of intestinal dialysis, Monograph. Rotterdam, Holland, M. Wyt and Sons, 1950.

PRACTICAL SUGGESTIONS IN THE PREPARATION OF A HIGH CALORIC LOW PROTEIN DIET

Marjorie Curry, Clinic Dietitian
and
June E. Thompson, Hospital Dietitian

Emulsion for intragastric drip according to Bull, Joekes and Lowe

Glucose	400	This is made in the pharmacy at the Cleveland Clinic. Given as continuous drip through nasal catheter. Use plastic tube.
Peanut oil	100	
Acacia	q. s. to emulsify, usually 25 Gm.	
Water	1 liter	
Vitamins		

The butter soup according to Borst

Sugar	150 Gm.	1775 calories, 2 Gm. protein. When divided over 6 portions of 100 ml. each portion will contain approximately 300 calories. Vitamins preferably parenteral.
Salt free butter	150 Gm.	
Flour	q. s. to make emulsion, usually 20 Gm.	
Water	Approximately 300 Gm.	
Coffee extract	q. s.	

Method of preparation: Mix sugar and flour together. Add enough water to make a paste. Add butter. Cook in double boiler, stirring constantly. When flour is well-cooked and starch taste disappears, gradually add water until total volume is 600 ml. Cook thoroughly, stirring constantly. Remove from heat and stir until cool. Add flavoring; strong coffee extract is appreciated most although lemon, vanilla, etc., may be tried. If properly made, the Borst butter soup should stay in emulsion, thin enough to drink from a cup. It should be divided in portions throughout the day; for example, 7 a.m., 9 a.m., 11 a.m., 3 p.m., 6 p.m., 9 p.m., each serving 100 ml. The patient should drink the soup at once, rather than postpone it. If he vomits, continue it. If the patient prefers the drink hot, heat only one portion at a time, otherwise emulsion may be destroyed.

One or more of the following "suggestions" may be supplemented at the time of the usual meals, or given to replace a portion of the butter soup. However, these should not be started before the patient has shown his cooperation in taking the butter soup.

Even if all ten of these suggestions were followed in one day, the patient would only get 22 Gm. of protein. Sometimes it is necessary to leave the butter out of some of the suggestions. Some patients can be allowed large amounts of fruit juice or Kool-aid with which the intake of sugar may be encouraged.

Suggestions to be used as supplements or substitutions for Borst butter soup

	Amt. in Gm.	Calories
1.		
½ cupful cooked rice	100	210
1½ squares butter	15	
2.		
½ cupful baked potato (contains 400 mg. potassium)	100	200
1½ squares butter	15	
3.		
1 zwieback (low salt)	8	90
2 teaspoons jelly	10	
½ square butter	5	
4.		
fresh tomato puree (canned may be used if salt is allowed)	75	265
1 teaspoon sugar	5	
3 squares butter	30	
5.		
fresh cooked celery (contains 225 mg. potassium)	75	275
3 squares butter	30	
1 tablespoon cream	15	
6.		
½ cupful boiled sweet potato (contains 200 mg. potassium)	100	380
3½ squares butter	35	
7.		
1 pancake	50	320
1 square butter	10	
3 tablespoons syrup (maple or white sugar syrup)	40	
8.		
½ cupful chocolate pudding (4.5 Gm. protein)	100	280
1 tablespoon whipped cream	15	
9.		
cinnamon toast		
1½ slices bread (4.5. Gm. protein)	45	340
2 squares butter	20	
4 teaspoons sugar	20	
10.		
½ cupful corn meal mush	100	220
2 squares butter	20	

SUBLUXATION OF THE CERVICAL SPINE

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SUBLUXATION of the apophyseal articulations of the cervical spine and narrowing of the intervertebral space may follow an injury to an intervertebral cartilage. This abnormal position of the apophyseal articulations is the result of instability in the involved region of the cervical spine.

Hadley[1] has pointed out that apophyseal subluxation in the lumbar region is capable of producing pain in three ways: (1) tension upon the capsular ligaments, (2) encroachment upon the size of the lumen of the intervertebral foramina, and (3) impingement of the ends of the articular processes against the pedicle above and the lamina below, respectively.

Encroachment upon the size of the lumen of the intervertebral foramen is likewise encountered in lower cervical subluxations since the anteroposterior diameter of the intervertebral foramen is smallest at points of maximum lordosis of the spine, namely the lower cervical and lower lumbar regions.

Semmes and Murphy[2] state that narrowing of the intervertebral disk can allow narrowing of the intervertebral foramina only in the vertical diameter; such narrowing is not sufficient to cause pressure on the nerve root unless the intervertebral space is completely obliterated and there is destruction of the adjacent surfaces of the vertebrae. In some cases, however, we believe that subluxation of the apophyseal joints develops and the narrowing of the intervertebral foramen is manifested in the anteroposterior diameter as well as in the vertical diameter. This abnormal alignment of the neck can be visualized readily in the lateral roentgenograms of the cervical spine. Definite forward migration of the head and cervical spine above the level of the cartilage injury is observed, with maximum angulation at this level. Since the posterior walls of the intervertebral foramina consist of the joints made by the articular processes, any forward displacement of these processes produces encroachment upon the foramen and reduces the clearance for the nerve. Furthermore, since flexion and extension of the neck are made by the vertebrae rocking at the articular facets and since the foramina are anterior to the facets, it is obvious that when the neck is bent forward there is a further reduction in the size of the foramen.[3] The oblique roentgenograms will show a narrowing of the intervertebral foramen at the level of the involved disk. Clinically the poker spine which is seen in the cervical and lumbar regions following nerve root pressure is probably an adaptive mechanism to increase the stability of the spine in these regions.

We are presenting 2 almost identical cases in which the abnormal position of the apophyseal articulations was so evident as to present a true subluxation and the patients received relief of pain and paresthesias only after a prolonged period of traction and restoration of the normal alignment of the neck.

(a) (b)

FIG. 1. Case 1. (a) Appearance before reduction of subluxation. (b) After reduction of subluxation and fusion.

Both patients had previously undergone operations of the cervical spine. In case 1 a protruded disk had been removed at the sixth cervical interspace 4 years before. In case 2 a protruded disk, partially osseous in character, had been removed from the sixth cervical interspace 15 months previously. In both patients, the head was carried in a forward position (figs. 1a and 3a), and the muscle spasm was so extreme that extension of the neck was impossible.

In each instance the lateral roentgenogram (figs. 2a and 4a) showed the forward migration of the head and cervical spine above the level of the subluxation and the angulation at the level of the subluxation.

Case Reports

Case 1. A 30-year-old white man was first seen on April 25, 1945, with the chief complaint of pain in the right shoulder and down the right arm to the elbow, of 2 months' duration. On examination tenderness was demonstrated over the spines of C_6 and C_7; pressure immediately lateral to the spines of C_6 and C_7 on the right aggravated the pain in the right shoulder and right arm. The patient also experienced slight weakness of grip in the right hand.

Past history revealed an injury to the neck at the age of 14, sustained when he was thrown forcibly against the top of an automobile. However, he experienced no disa-

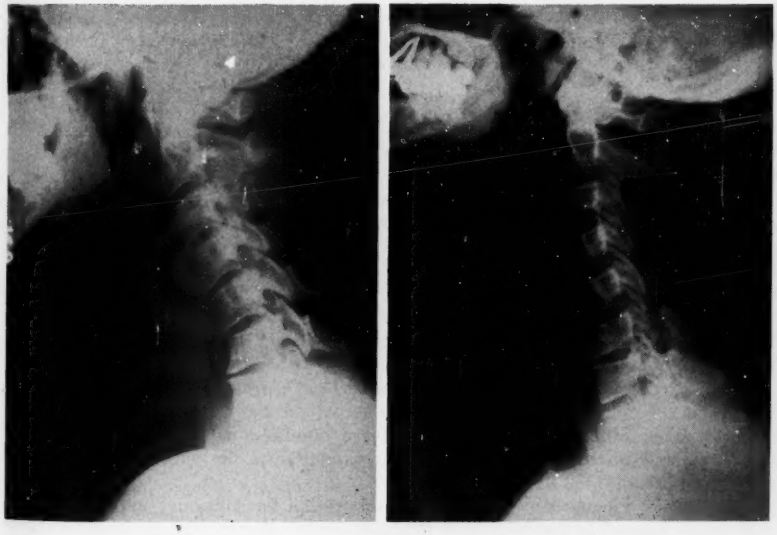
bility at that time. He subsequently slipped and fell on the ice, striking his left hip and left shoulder about 3 weeks prior to the onset of the present complaints.

During a 6 week period following his first visit, the patient developed numbness and hypesthesia of the right thumb and index finger and noticed the onset of weakness in the right arm, accompanied by fibrillary twitchings in the right deltoid and pectoral muscles. He also showed moderate diminution in the triceps reflex on the right. Lumbar puncture was normal. The patient was admitted to the hospital on June 3, 1945, and a protruded intervertebral disk was removed between C_6 and C_7 on the right. He had an uneventful postoperative course and was discharged on the fifteenth postoperative day with relief of his pain and numbness, but with definite diminution of the triceps reflex on the right. He remained symptom-free for 4 years until May 15, 1949, when his head dropped backward suddenly while riding on a cart and he felt a snap in the neck.

The patient was re-admitted to the hospital 3 weeks later with the identical signs and symptoms which had existed before the removal of his ruptured intervertebral disk 4 years previously.

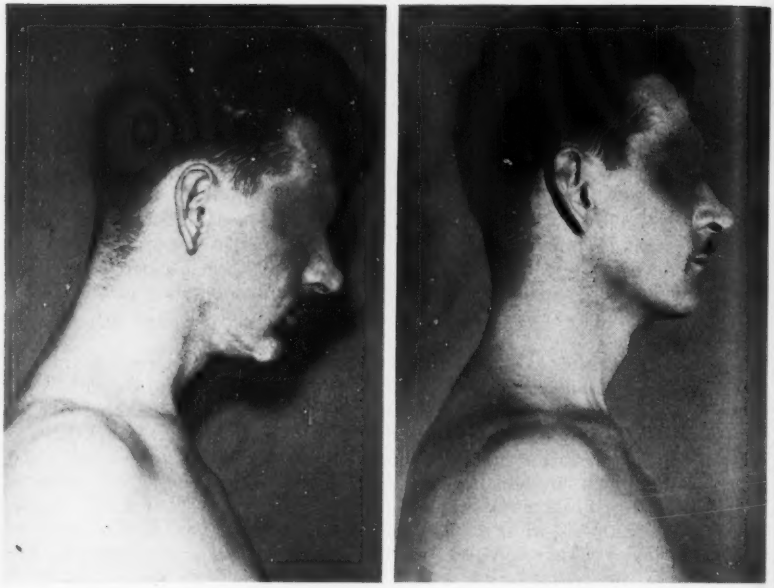
His pain gradually subsided and was almost entirely relieved by cervical traction for 12 days. An interlaminar cervical fusion was performed from C_5 to C_7, with osteoperiosteal bone graft from the tibia. The patient was discharged on the thirty-seventh postoperative day with a cervical brace which he wore for 8 months. X-rays (fig. 2b) were made 9 months after operation and showed satisfactory fusion of C_5 to C_7 and clinically he presented no symptoms with the exception of slight stiffness in the neck. The head was carried in a normal position (fig. 1b).

Case 2. A 36-year-old white man was first observed on February 2, 1948, with the principal complaint of increasing pain in the right shoulder of 5 months' duration. The



(a) (b)

FIG. 2. Case 1. (a) Lateral x-ray showing subluxation. (b) Showing reduction of subluxation and fusion.



(a) (b)

FIG. 3. Case 2. (a) Appearance before reduction of subluxation. (b) After reduction of subluxation and fusion.

pain was worse over the posterior superior border of the trapezius, the lateral portion of the pectoral muscles and over the extensor muscles in the right forearm—so severe that the patient was unable to sleep nights.

On physical examination flexion and lateral motions of the spine aggravated the right shoulder and arm pain. There was slight weakness of grip in the right hand and point tenderness to the right of the spines of C_6 and C_7 and over the posterior superior border of the trapezius on the right. The right radial reflex was absent and the right triceps moderately diminished.

He was admitted to the hospital and cervical traction afforded relief of the pain in the right shoulder in 6 days; however he experienced some numbness in the right index finger. Lumbar puncture was normal.

At operation a disk protrusion was found at C_6, C_7, which was partially osseous in character. The following day the patient reported the best night's sleep experienced since the onset of the present condition; however, numbness persisted in the right index finger. He was discharged on the fifteenth postoperative day with a cervical brace, which he wore for 3 months.

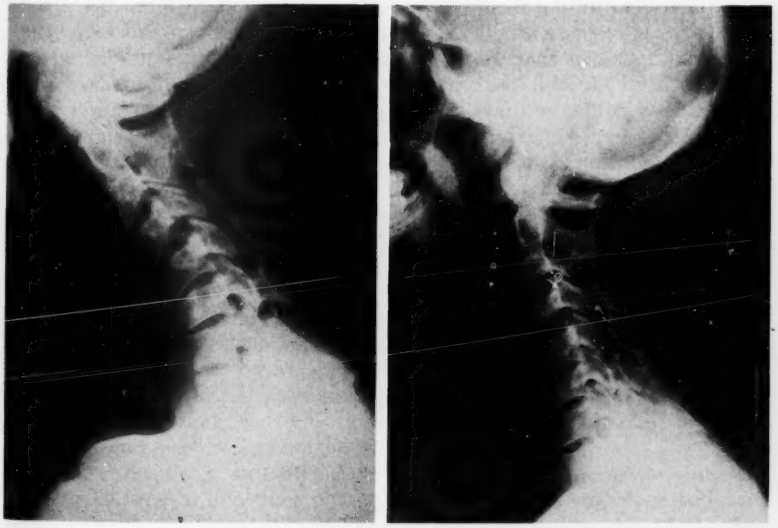
He remained symptom-free for 15 months, except for subjective numbness in the right index finger. He then fell while working and received a mild injury to the right chest wall, at which time there was recurrence of pain in the right shoulder and right arm. He was re-admitted to the hospital and was almost completely relieved of pain following restoration of the normal alignment of his cervical spine after a period of

2 weeks in traction. A fusion was done from C_4 to C_7 with osteoperiosteal graft from the tibia. He had an uneventful postoperative course and was discharged on the twenty-ninth postoperative day with a cervical brace which he wore for 7 months. His range of motion improved and he returned to his work as an electrician 9 months after fusion. Cervical roentgenograms 1 year after operation showed fusion from C_4 to C_7 (fig. 4b). The head was carried in a normal position after fusion (fig. 3b).

Discussion

When the instability of the cervical spine following injury of an intervertebral cartilage is of a mild or moderate degree, and narrowing of the intervertebral foramina is only in the vertical diameter, conservative treatment is sufficient to effect relief of pain or paresthesias. The conservative treatment which we recommend is directed toward correcting the abnormal alignment of the cervical spine and maintaining normal alignment until stability can be accomplished by muscle-strengthening exercises. The patient is hospitalized and cervical traction begun by means of a Sayre sling with four-pound weight attached. Traction is employed for 1 hour three times daily and gradually increased to 1½ hours four times daily over a period of 4 to 6 days. The patient also receives daily physical therapy to the neck to overcome muscle spasm. Many patients require 2 weeks or more of such treatment before experiencing relief of pain or paresthesias.

In the cases we have presented, the instability was so pronounced that a



(a) (b)

FIG. 4. Case 2. (a) Lateral x-ray showing subluxation. (b) Showing reduction of subluxation and fusion.

true subluxation developed and narrowing of the intervertebral foramen in the anteroposterior diameter, as well as the vertical diameter, resulted in severe nerve root pressure. We believe that, in patients presenting this degree of instability, a fusion is necessary to maintain the normal alignment after reduction of the subluxation has been accomplished.

References

1. Hadley, L. A.: Subluxation of apophyseal articulations with bony impingement as cause of back pain. Am. J. Roentgenol. **33**:209 (Feb.) 1935.
2. Semmes, R. E. and Murphy, F.: Syndrome of unilateral rupture of sixth cervical intervertebral disk, with compression of seventh cervical nerve root; report of 4 cases with symptoms simulating coronary disease. J.A.M.A. **121**:1209 (April 10) 1943.
3. Nachlas, I. W.: Scalenus anticus syndrome or cervical foraminal compression. South. M. J. **35**:663 (July) 1942.

IDIOPATHIC LETHAL GRANULOMATOUS ULCERATION OF THE NOSE AND FACE*

Report of Six Cases

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REPORTS have occasionally appeared in the literature concerning a group of unusual and ultimately fatal cases characterized by nonspecific granulomatous ulcerations of the upper respiratory tract and face. We shall review these clinical features and report 6 cases which we have observed at the Cleveland Clinic over a period of 15 years; 3 of these have terminated in death. In 2 of the 3 patients living the general course has been a gradual decline, characterized by symptoms strikingly similar in various stages to those cases in which the patients died. At the present time one of these patients is apparently well and entirely free from all symptoms. Another is entering the stage of early necrotizing lesions of the nasal septum, while the third is approaching the terminal phase.

In none of our cases has an etiologic agent been found which might possibly account for the severity and relentlessly progressive nature of this affliction despite exhaustive chemical, bacteriologic, and microscopic examinations. Thus we are unable to contribute further to previous investigations of the etiology of these peculiar and devastating lesions. Williams,[1] in his excellent presentation, has summarized the possibilities, many of which we have considered from time to time. That the disorder is perplexing is evidenced by the diversity and multiplicity of diagnostic procedures and therapeutic approaches which have been utilized in an effort to bring the lesions under control.

The onomatology applied to this affliction has varied with different authors. It has been termed "lethal granulomatous ulceration of the midline facial tissues" by Williams,[1] "granulomatous ulcer of the nose and face" by Hoover,[2] "chronic granulomatous ulcer of the nose of unknown cause" by Isbell,[3] "chronic infectious granuloma of the nose" by Lierle,[4] "gangrenous osteomyelitis of the paranasal sinuses" by Lewy,[5] "progressive lethal granulomatous ulceration of the nose" by Stewart,[6] "malignant granuloma of the nose" by Woods,[7] and "mutilating granuloma of the nose and face with fatal ending" by Wood.[8] We believe the term "idiopathic lethal granulomatous ulceration of the nose and face" represents the entity most accurately.

Stewart[6] has given an edifying description of the course of the disease in which he classifies it into three phases based upon symptomatology and pathologic progression. He calls the first the prodromal stage; the second the stage of active disease and the third the terminal stage.

*Awarded first prize for residents at the annual Spring Meeting of the Cleveland Otolaryngological Society, April 4, 1951.

He observes that the prodromal stage is characterized by intermittent nasal obstruction often accompanied by postnasal discharge and a watery or serosanguineous rhinorrhea. Occasionally, however, the disease may be initiated by the appearance of a superficial ulceration in the nasal vestibule or nasal septum. In some patients a history of pre-existing infection of the paranasal sinuses can be obtained. Surgical procedures in the nose usually conclude unfortunately. A perforation of the septum may be anticipated following a submucous resection. The prodromal stage may endure from several weeks to several years.

The "period of active disease" is Stewart's[6] application to the second stage. In our experience this phase is usually of 10 to 18 months' duration. The characteristic feature is the appearance of a small, shallow ulcer on the nasal septum, inferior concha, floor of the nose or palate, covered with an inspissated crust which, on removal, reveals a denuded surface. The discharge has a fetid odor and is purulent or sanguinopurulent. In general, the lesions tend to invade the interior of the nose from the roof of the mouth, and from inside of the nose erode onto the face. Early in the involvement of the facial tissues, the nose and paranasal structures become indurated and swollen. As the lesion progresses, the palatal, nasal, and malar bones undergo necrosis and sequestrate. Abscesses may develop in the soft tissues. The temperature is irregular, being normal or slightly elevated. The blood condition is of little diagnostic aid. Leukocyte count may be normal, slightly elevated, or show a mild leukopenia; the differential count varies but it is usually normal or returns to normal on repeated examination. Agranulocytosis has never been found, and septicemia is uniformly absent. The most striking observation of this second phase is that, despite the apparent gravity of the destructive lesion, the patient enjoys a sense of well-being except for varying degrees of weakness and lassitude.

The prominent features of the terminal stage, as set forth by Stewart,[6] are the evident exhaustion of the patient and the extreme mutilation of the advancing lesions. The eyelids are swollen with a purulent discharge exuding from between the lids. The face may be exceedingly disfigured with the development of a large central aperture, through which the violence of the destructive process is readily ascertained. The appearance of the involved area defies accurate description. A fetid odor of putrefaction exudes from the gaping lesion, the margins of which are indurated with rolled, heaped-up tissue. The nasal septum, nasal conchae, and the hard and soft palates may have been obliterated. Often the lateral walls of the nose have been completely eroded baring the pyriform aperture and malar bones. The pharynx and larynx may be extensively necrosed. In the central area of the face only a portion of the fleshy dorsum of the nose may remain; in other cases even this pedicle disappears. Only the tongue and basisphenoid are uniformly spared. The remaining exposed surfaces lining the ulcer are covered with a dirty brown or greenish-brown heavy crust. In most cases there is little oozing through this crust. Recurrent hemorrhage is often troublesome at this stage due to erosion through blood vessels, and this complication may cause sudden death. Usually, however, the fatality results from exhaustion and inanition with terminal temperatures ranging up to 106 or 107 F.

A constant, but unaccountable, observation throughout the entire course of the disease is the complete lack of effective resistance by the usual defensive mechanisms.

Williams[1] feels that the granuloma formation is the "stereotyped defensive mechanism by which the body resists invasion by micro-organisms which are poor toxin producers." He believes that dysfunction of the immunity mechanism with development of localized Arthus phenomena and periarteritis nodosa are the essential factors in granulomatous reaction.

Incidence

Idiopathic lethal granulomatous ulceration of the nose and face affects primarily the age groups between the late second and the seventh decades. Only 2 cases have been reported in children. Men are stricken in the proportion of 20:1 over women.[2] Our series consists of 4 men and 2 women with ages ranging from 17 to 53.

Pathology

The following report of a typical biopsy specimen taken for microscopic examination from the patient in Case 3 was given by Dr. John B. Hazard, pathologist at the Cleveland Clinic.

"Fragments present broad zones of necrosis. Viable tissue is comprised of a mucosal fragment, noticeably infiltrated by lymphocytes, plasma cells, some neutrophils and eosinophils, and with rather frequent histiocytes. The latter, in one section, appear to form variable-sized accumulations without the appearance of typical tubercles. Histiocytes and fibroblasts marginate zones of necrosis. Occasional mitoses are present, apparently in histiocytic cells. Giant cells of foreign body or Langhans' types are not evident. In one section there are occasional small epithelial islands as well as glandular structures. Necrosis is of infarct and coagulation types. There is deposition of fibrin or fibrinoid material in places.

"Examination of sections stained by Gram—Weigert, Giemsa, and acid-fast methods fail to reveal organisms.

"Diagnosis: Chronic granulomatous inflammation; necrosis. Etiologic agent not apparent. Note: Inflammatory response is rather unusual due to the frequency of histiocytes and the tendency to grouping of these cells. The process does not resemble any of the usual infectious granulomata."

It is interesting to note that, because of the unusual character of the microscopic picture, these sections were later sent to the departments of pathology at North Carolina, Vanderbilt, and Columbia Universities where they were examined by several members of each department. These pathologists were unable to agree on a definite diagnosis. Opinions varied between granulomatous inflammation of unusual type and neoplastic disease.

Diagnosis

Diagnosis of idiopathic lethal granulomatous ulceration of the nose and face is made by history, clinical findings, and exclusion of other diseases causing similar lesions. Those disorders to be eliminated are listed in the following table.

DISEASES TO BE EXCLUDED IN DIFFERENTIAL DIAGNOSIS

1. Syphilis
2. Tuberculosis
3. Malignant disease
4. Fungus infections
5. Histoplasmosis
6. Leukemia
7. Agranulocytosis
8. Diabetic gangrene
9. Noma
10. Erythema multiforme
11. Leprosy
12. Glanders
13. Anthrax
14. Tularemia
15. Myiasis
16. Yaws
17. Leishmaniasis
18. Postencephalitic ulcer (trophic)
19. Mycosis fungoides
20. Wegener's disease

Report of Cases

Case 1. A white man, aged 31, was first seen in November 1942. He gave a history of recurrent generalized small skin lesions of 10 weeks' duration. About 5 weeks previously he noted the onset of purplish areas on his back which gradually increased in size.

Examination revealed a well-developed and nourished patient in no acute distress. His temperature was normal with a pulse rate of 86 beats per minute and blood pressure of 160/86. The only significant finding was a generalized papular skin rash in which some of the more advanced lesions had ulcerated with resultant serosanguineous discharge. These lesions were of match-head size. In addition there were two larger purplish ulcerations in the left subscapular area. The Kahn test was 4 plus. The patient gave a history of a penile lesion contracted 5 years previously. The papular ulcerations on the body, however, did not have the appearance of late syphilis. The condition was diagnosed as "tuberculids" after a tuberculin skin test proved positive. Antisyphilitic therapy in the form of bismuth subsalicylate and potassium iodide, and tuberculin therapy were initiated simultaneously. Roentgenographic examination of the chest was negative. Blood studies revealed an erythrocyte count of 5,150,000 per cu. mm., hemoglobin concentration of 89 per cent, leukocyte count 8000 per cu. mm. with differential proportions of neutrophils 64 per cent, lymphocytes 31 per cent, monocytes 4 per cent, eosinophils 1 per cent. The sedimentation rate was 0.27 mm. per minute.

The skin lesions appeared to progress despite therapy. Potassium iodide was discontinued, and topical applications of ammoniated mercury ointment were employed. When continued deterioration of the patient's conditions was noted, a biopsy specimen was taken from one of the lesions on the back. The pathologic diagnosis was "inflammatory tissue."

The patient was referred to the Department of Otolaryngology 1 month following his first visit. His complaints at that time were alternate nasal obstruction of 2 years' duration, chronic hoarseness for 3 months, a sensation of pressure beneath the right eye for 1 month, and daily epistaxis for 2 weeks. Examination of the nose and throat

revealed bilateral choanal obstruction due to hypertrophy of the posterior ends of the interior turbinates. Granular, hemorrhagic areas covered with yellowish-green crusts were present in the nasopharyngeal vault. The vocal cords and subglottic area were diffusely injected and edematous. Clinically, the lesions appeared to be syphilitic or tuberculous in origin.

Mapharsen was added to the antisyphilitic regimen. Repeated sputum examinations were negative for acid-fast organisms. Stereoscopic x-rays of the chest were normal. Over a period of the next several months the patient failed to show general improvement, though there were short periods of mild remission between exacerbations. The entire mucosa in both nasal fossae gradually became involved with granulomatous lesions, and epistaxic episodes increased. A biopsy specimen was removed from the granulomatous area, but the pathologic report was inconclusive except for "inflammatory tissue." A skin test for histoplasmosis was negative. As the disease progressed the patient's throat became sore and he developed hemoptysis. Seven months following his initial visit the patient was admitted to the hospital for intensive sulfonamide therapy and 2 days later developed severe cramping pains with ecchymoses and edema in the legs, ankles, and feet bilaterally. The pain required heavy narcosis for adequate analgesia. The edematous ecchymotic areas on the lower extremities resembled "erythema multiforme" lesions measuring up to 1 cm. in diameter. The Frei test was negative. Sulfathiazole and sulfadiazine therapy were discontinued and neoprontisil was instituted. About 1 month after admission he developed severe diarrhea with temperature to 105 F. An unsuccessful attempt was made to obtain penicillin from the National Research Council.

By this time the patient had complete aphonia. He was given x-ray therapy to the larynx and, despite postradiational nausea, showed rapid subjective improvement of his voice. His erythrocyte count was 2,800,000 cells per cu. mm. with a hemoglobin concentration of 44 per cent. After receiving two transfusions of whole blood his condition was so much improved that he was discharged from the hospital a few days subsequently following a confinement of about 10 weeks. Clinical examination 2 weeks later disclosed that the patient had experienced no further episodes of hemoptysis. Moderate crusting was still present in the nose, but the nasopharynx and larynx appeared almost normal. In the interim following discharge from the hospital the patient had developed polydipsia and polyuria without hematuria. Urine examination revealed a trace of albumin. Microscopic study showed many erythrocytes, leukocytes, and casts. The Kahn test was negative, and the red blood count was 3,500,000 per cu. mm.

Four weeks later the patient was again examined in the Department of Otolaryngology where he was found to have had a severe exacerbation of his previous upper respiratory symptoms. Intermittent hemoptysis and pronounced hoarseness had recurred. The crusting in the nose, pharynx, and larynx was heavy with a fetid odor. Despite his obvious deterioration the patient enjoyed a sense of well-being and had gained 25 pounds since his discharge from the hospital. He was placed on potassium permanganate nasal sprays every 2 hours. Two days later the patient was stricken with acute abdominal pain in the umbilical area with radiations to the epigastrium and hypogastrium. His temperature rose to 102 F. A spinal puncture was negative. Urine examination again revealed casts, red, and white cells in heavy concentrations. On readmittance to the hospital the diagnosis was chronic glomerulonephritis with secondary anemia. The purpuric lesions of the skin recurred. A gastrointestinal series revealed a "spectacular lesion consisting of generalized, soft infiltration, probably edema, of the upper small intestine, suggesting numerous possibilities." Studies of the sternal bone marrow were negative. Although he was given further whole blood

transfusions and neoarsphenamine his condition rapidly became hopeless and he died 3 weeks after admission.

A necropsy was performed, and the final pathologic diagnoses were: chronic glomerulonephritis with superimposed acute pyelonephritis; acute necrotizing arteritis involving kidneys, skeletal muscle, lungs, esophagus, and small intestine; nonspecific granulomatous ulcers of the nose, nasopharynx, pharynx, and larynx; acute pericarditis and terminal bronchopneumonia.

Case 2. A 26-year-old white man was first observed because of swelling, pain, and obstruction of the left nasal cavity, accompanied by headaches and fever.

Two years prior to admission, while stationed in the Azores, he had experienced daily febrile episodes. He was told that he had asthma and "bad nerves," and was discharged from service because of these complaints. He continued to have daily elevations of temperature to 104 F.; these had been accompanied by chills except when the fever exceeded 102 F. For one year previous to our examination he had noted headaches limited to the entire left side of the head, relieved by lying down for about 5 minutes. There were no associated episodes. Nasal swelling followed a blow on the nose one month prior to entry. Previously he had experienced partial nasal obstruction on the left which subsequently increased in severity. Constant right subcostal pain had been present for 4 years; cholecystograms and barium enema studies had been negative. There were no other complaints referable to the gastrointestinal system. He had experienced seasonal pollinosis.

Physical examination revealed a fairly well-developed man weighing 158 pounds (normal 165). His temperature was 100 F., pulse rate 108 beats per minute, blood pressure 120/88. The nose was enlarged externally and somewhat deformed, the swelling simulating a hematoma. On the left near the base a light red, poorly demarcated, scaly plaque was evident. The lesion extended over the bridge and for a slight distance on the right of the nose. There was chronic edema of infraobital tissues. No rolled border was present on the inflammatory area. The nasal septum was noticeably deviated. The left naris was tender and completely obstructed with warty excrescences and granulation tissue; the right fossa was 90 per cent obstructed. The tonsils were enlarged and the soft palate injected. Several tender right submaxillary and right deep cervical nodes were palpable. There was slight tenderness to deep bimanual palpation of the right flank.

A urinalysis was negative. The erythrocyte count was 5,200,000 cells per cu. mm. with a hemoglobin concentration of 14. Gm. per 100 cc.; the leukocyte count was 13,850 cells per cu. mm. with 71 per cent neutrophils. A blood sugar was 112 mg. per cent. Serology test was normal; a lumbar puncture revealed normal dynamics and spinal fluid.

He was treated as an outpatient for 3 months and given local applications of hot magnesium sulfate packs. Two months before hospital entry he experienced pronounced pain, swelling, and warmth of both knees for which he was given sulfadiazine. Although the joint pains subsided, his temperature continued to reach 103 F. Quinine had no effect, and the swelling over the nasal bones persisted and became worse.

Three months after the first visit, the patient was admitted to the Cleveland Clinic Hospital for penicillin therapy for the fever and the verrucous lesion of the nose. At this time there was redness and swelling over the left side of the nose and infraorbital area without a break in the skin or rolled margins. The acute swelling of the infraorbital tissues had existed for 10 days. A large, nontender lymph node was present in the left submaxillary region and a similar node was palpated in the left axilla.

Urinalysis was again negative. The white cells numbered 11,900 per cu. mm. with 70 per cent neutrophils and the red cells 5,200,000 per cu. mm. Examination of the

feces was negative for ova or parasites. An agglutination test was negative for tularemia. A heterophil antibody test was positive at dilution 1:16. Blood culture was negative. No malarial parasites could be demonstrated. A brucellergen skin test was negative. Nasal cultures were positive for nonhemolytic streptococcus, Staphylococcus albus, and diphtheroid bacilli; on two occasions organisms reported as K. L. bacilli were found and in one instance pseudodiphtheria organisms, "Hoffman's bacillus," were cultured. Roentgenographic examination of the sinuses showed an increased density at the inferior angle of the right antrum. The left antrum, the sphenoid, ethmoid, and frontal sinuses were negative. Examination of the nose revealed a slight deviation of the nasal septum to the left without evidence of old fracture or osteomyelitis. The right antrum contained thickened membrane. Roentgenographic studies of the skull and chest were normal. Biopsy specimens taken from the skin of the left side of the nose and a lymph node in the right axilla were reported as "chronic inflammation, granulomatous type."

While in the hospital the patient received penicillin every 3 hours (50,000 units) for 1 week without effect on the fever, which followed a septic course. Two intravenous injections of neoarsphenamine were given at weekly intervals without relief. Fifty thousand units of diphtheria antitoxin were also administered without change. The patient's headaches continued, accompanied by stiffness of the neck. He gradually became worse with increased swelling and tenderness of the nose, enlargement and tenderness of the cervical, axillary, and inguinal nodes, and continued sepsis. The patient remained in the Cleveland Clinic Hospital for 6 weeks, at the end of which time he was transferred to a veterans' hospital. There he continued a febrile course with progression of the local lesion and ulceration of the nares. He died 3 weeks after admission. No autopsy was performed.

Case 3. A 17-year-old white girl was examined because of chronic nasal obstruction, excessive nasal crusting, and episodes of epistaxis which had been present since a severe case of scarlet fever at the age of 5. Two years previous to this visit she developed aphonia and extreme dyspnea. She was admitted to a hospital where her symptoms subsided under oxygen therapy. Her aphonia continued following discharge, and 3 months later she was again admitted to the hospital because of recurrent dyspnea. A tracheotomy was performed for tumor of the larynx. A biopsy of the laryngeal tumor was reported as squamous cell papilloma. Despite continued aphonia she was able to be decannulated after 2 months. Eleven months later she developed "flu and virus pneumonia" with subsequent dyspnea and was again hospitalized for 30 days. The vocal cords were extensively scarred, and the papillomatous process extended into the trachea. The laryngeal cicatrix was partially removed with immediate relief of the patient's dyspnea and she was referred to another hospital for evaluation. Her trouble was considered due to fungus disease because she responded well to potassium iodide therapy, whereas the laryngeal edema was not affected by sulfonamide or penicillin therapy. Three months prior to our examination the patient developed febrile episodes attributed to the apparent infectious process in the nose. Although there was no objective improvement in these lesions following bed rest, nasal sprays, and penicillin, the patient felt much better temporarily. Five weeks before she was referred to the Clinic a slightly tender and painful external swelling developed in the left ethmoidal area.

Physical examination revealed a slightly emaciated, but well-developed and nourished young woman in no acute distress. Her temperature was 98.6 F., pulse rate 80 beats per minute, blood pressure 120/70. Both nasal fossae contained boggy, granular-appearing turbinates covered by a greenish, tenacious crust which, when removed, revealed raw, denuded bleeding areas. A papillomatous type growth was evident in the left naris. Externally, a slightly reddened area of swelling without break in the skin was noted in the left ethmoidal region. Foul smelling purulent discharge was present in the

nasopharynx. The larynx was infantile and noticeably edematous and injected. The remainder of the general physical examination revealed no significant abnormalities.

A urinalysis was negative. Hematology studies revealed 4,100,000 erythrocytes per cu. mm. with a hemoglobin concentration of 11.5 Gm. per cent, 3,600 leukocytes per cu. mm. The differential proportions were: 45 per cent neutrophils, 37 per cent lymphocytes, 10 per cent monocytes, 1 per cent eosinophils, and 7 per cent nonfilamented neutrophils. The sedimentation rate was elevated to 1.35 mm. per minute. A blood sugar was 96 mg. per cent. The serology was normal. The Frei test was negative as were agglutination tests for tularemia, typhoid, and paratyphoid; tuberculin and histoplasmin skin tests were negative. Blood culture was sterile. Cultures from the nasal lesions revealed the presence of nonhemolytic streptococcus, Staphylococcus albus, diphtheroids, Micrococcus catarrhalis, spirochetes, and fusiform bacilli. A biopsy specimen removed from the nose was diagnosed as "chronic granulomatous inflammation; necrosis. Etiologic agent not apparent."

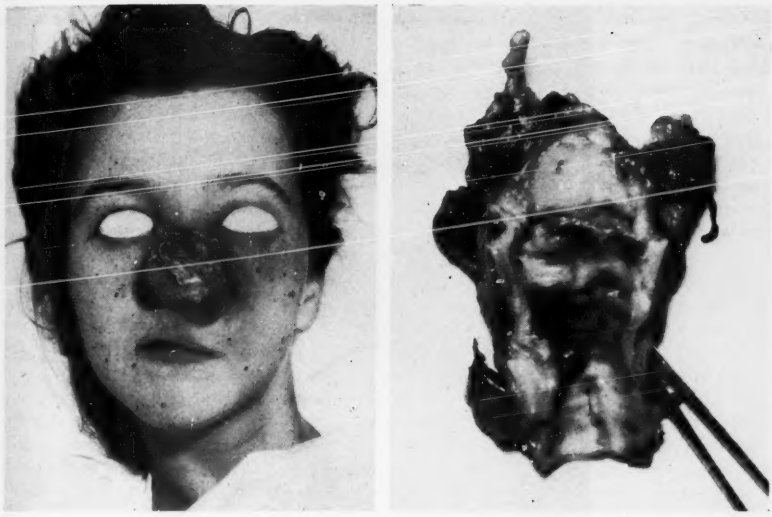
The patient was admitted to the Cleveland Clinic Hospital for further evaluation and treatment. She was given massive doses of penicillin and streptomycin together with sulfadiazine and urea (10 Gm. four times a day). Inflammatory doses of x-ray therapy were given to the facial and left cervical areas. The patient's condition continued to deteriorate with gradual increase of fever which spiked to 104 F. The nasal lesions showed no signs of regression. After 3 weeks in the hospital she had lost 18 pounds; her total weight was 88 pounds. At this time she had developed a severe leukopenia (1,500 white blood cells per cu. mm.) and anemia (9.0 Gm. per cent on hemoglobin concentration). She was given two whole blood transfusions, neoarsphenamine, and four injections of nitrogen mustard. The disease was refractive to all therapy, and the patient continued a rapid downhill course, showing evidence of complete exhaustion. Her terminal temperature rose to 106.4 F., and she died 6 weeks following admission (fig. 1a and b).

An autopsy was performed and the final diagnoses were: necrotizing and ulcerative rhinitis, nasopharyngitis, and laryngitis with necrosing lesion of the hard palate; chronic inflammation of the sphenoid and left ethmoid sinuses; pronounced granulopoietic hypoplasia of bone marrow; terminal bronchopneumonia of the right lower lobe and partial atelectasis of the left lower lobe. The internal organs were entirely normal, showing no evidence of primary or secondary manifestations which could explain the involved tissues of the face and upper respiratory tract.

Case 4. A 19-year-old white youth was referred to the Cleveland Clinic because of a history of recurrent head colds and a progressive swelling under the right eye and root of the nose, symptoms which had been present for 9 months; there was no history of illness or injury at onset. Three months prior to his first visit he had consulted a local physician for treatment of these symptoms after which a right intranasal antrotomy, ethmoidectomy and submucous resection were performed. A week later the patient underwent a tonsillectomy. Two hundred roentgen units of x-ray therapy were given on the face over the swollen area. Six weeks later the patient was readmitted to the local hospital because of sore throat, dysphagia, and odynophagia. He was found to have induration of the hard and soft palates and an ulceration in the oropharynx. A biopsy taken from the latter area was reported as "epidermoid carcinoma, grade I." Subsequent biopsy specimens were negative for neoplasm.

All blood studies had been negative. Cultures from the pharyngeal lesion had revealed the presence of "streptococci." He had been given penicillin, mercurochrome, and iodine drops without relief. There had been no febrile episodes.

Otolaryngologic examination disclosed crusting of the right nasal vestibule with



(a) (b)

FIG. 1. Patient in terminal stage showing (a) extensive necrosis of nose and edema of facial tissues on left; three weeks prior to photograph patient had no ulceration on external surface; (b) ulceration and granulation of vocal cords in larynx opened posteriorly.

mucopurulent discharge in the right nasal cavity. The mucous membrane was significantly injected. Inspissated mucous filled the nasopharynx. In the tonsil fossae and oropharynx multiple, small, pitted, shallow, bluish-red ulcers were present. A large multiform ulceration of similar appearance was found on the hard palate and several smaller ulcerations involved the soft palate. Beneath the right eye and involving the inner canthus was a swollen area covered with a brownish crust. Nonpitting edema extended laterally to the lateral canthus along the lower eyelid and a slight edema of the upper lid was noted. The lesions were nonpainful but slightly tender. No lymphadenopathy was present. The temperature was 100 F., with a pulse rate of 160 beats per minute (fig. 2).

A urinalysis was negative. Blood studies revealed 5,500,000 red cells per cu. mm.; the hemoglobin content was 13.5 Gm. per cent; 6,700 white cells per cu. mm. with essentially normal differential proportions. The sedimentation rate was elevated to 0.96 mm. per minute. Serology was negative. Roentgenographic examination showed clouding of all sinuses on the right; the chest was normal. Agglutination series for undulant fever, typhoid, paratyphoid, and tularemia were negative, as were the Frei test, tuberculin and histoplasmosis skin tests. Blood culture was sterile. Smears and cultures from the lesions on the face and nasal mucuous membrane revealed the presence of Staphylococcus aureus and diphtheroids. Biopsy specimens taken from the face and nasal areas were diagnosed as atypical granulomatous inflammation with pseudoepitheliomatous hyperplasia.

The patient was admitted to the Cleveland Clinic Hospital for antibiotic and chemotherapy consisting of dihydrostreptomycin, duomycin, and sulfadiazine. After

FIG. 2. Showing chronic ulceration of inner canthus and lower eyelid; ulcer of 6 weeks' duration.

6 weeks confinement the facial lesions had improved somewhat but the oral lesions appeared slightly worse. As the prognosis was apparently hopeless, he was discharged. After the patient returned home he consulted a local physician, who, by his own admission, has "cured several hundred cases of external cancer after surgery and x-ray treatments had failed." This doctor reported to us that he cured the facial lesion as follows: The skin surrounding the lesion was divided by sharp dissection "to a point one-half to two-thirds of the distance behind the ulcer. This leaves a flap behind which is placed cotton containing 30 per cent arsenous acid in diathane ointment. In a few days the entire ulceration sloughs away leaving healthy granulation tissue." He sent photographs to show the completely healed area which left only a minor cosmetic defect. The oral lesions proved much more refractive to therapy. The local doctor tried ultraviolet light and later zinc chloride ointment without success. Then he employed fuming mitric acid directly on the ulcers, but discontinued this form of treatment because of the intense irritation caused by inhalation of the fumes. He then applied 25 to 50 per cent lactic acid. This agent ate through the palate, but, according to the doctor, healthy granulation appeared here also with ultimate healing of the lesions; the palate, however, was largely destroyed. The patient was subsequently fitted with a prosthetic appliance. He gained 37 pounds in a short time. When last reported 2 years ago he was apparently well and entirely free from symptoms. We have been unable to obtain further progress records as contact has been lost, unfortunately, with both the patient and the local doctor.

Case 5. A 53-year-old white man was seen in the Department of Otolaryngology

with a history of chronic nasal obstruction and troublesome brownish and greenish crusting in the nose of 9 years' duration. The onset of his illness followed a gastroenterostomy after which a Wangensteen tube was introduced through the nose and left in place for several days. Shortly afterwards he consulted his local physician who prescribed nose drops and nasal packs. He had no further treatment until 6 years later when he was treated with nasal irrigations and sprays. Two years subsequently and 1 year prior to his first Clinic visit, he experienced anosmia. Three months before entry a fetid odor developed which had gradually become increasingly offensive. One month later he underwent a right Caldwell-Luc procedure with removal of polyps. Chloromycetin was administered with no alleviation. Four days prior to our examination he developed epistaxis from the left nasal fossa.

Otolaryngologic examination revealed a foul smelling greenish-brown heavy crust covering the entire mucosal surfaces of both nasal fossae and the nasopharynx and a large anterior septal perforation with a posterior erosion extending along the vomerine ridge for a distance of about 2 cm. behind the larger anterior perforation. The right inferior turbinate and lateral nasal wall had been completely eroded baring the pyriform aperture on that side. A peculiar type of granulation tissue was present in the right side of the nasopharynx. The crusts were tenacious and when pulled away left bleeding areas in the underlying tissue. There was a slight swelling on the face lateral to the nose without discoloration or dehiscence of the skin. Despite the obvious gravity of his condition the patient was not uncomfortable. His temperature was normal (fig. 3).

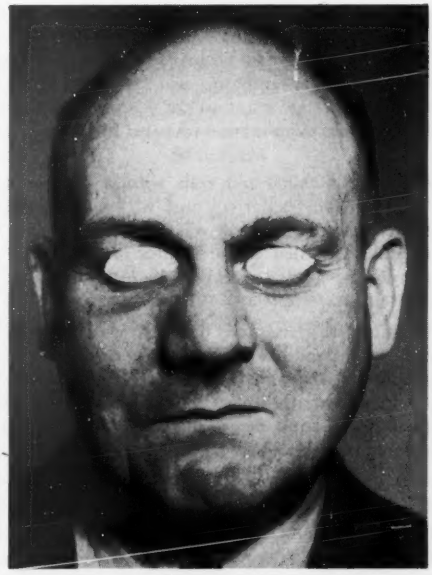


FIG. 3. External swelling of right lateral wall of nose. Internal ulceration extensive with erosion of nasal septum, middle and inferior turbinates, and lateral nasal wall baring the pyriform aperture.

Roentgenographic studies of the paranasal sinuses revealed a cloudy right antrum. The other sinuses were normal. Blood examination revealed 4,700,000 red cells per cu. mm. with a hemoglobin concentration of 11.5 Gm. per cent; 4,500 leukocytes per cu. mm. with normal differential proportions. Serology was negative, and blood sugar within normal limits. Cultures from the nose revealed the presence of Streptococcus hemolyticus, Staphylococcus albus, and the colon bacillus. A biopsy specimen was reported as "chronic inflammation."

The patient was treated with salt and soda nasal irrigations, oil of Thuja and Blandine compound sprays, and cortisone spray in the dilution of 1:4. He showed no improvement on this regimen. More recently he has been hospitalized and has improved noticeably on adrenocorticotropic hormone (ACTH). At present, however, complete remission of the lesions has not occurred following 2 weeks of this therapy.

Case 6. A 42-year-old white woman was first seen in the Department of Otolaryngology because of chronic nasal congestion, postnasal discharge, pressure sensations over the bridge of the nose and frontal areas, and frequent head colds of 8 years' duration. All of these symptoms were aggravated by inclement conditions of the weather. Otolaryngologic examination revealed hypertrophy of the nasal conchae with pale, edematous mucosa, hypertrophy of the adenoid and a devitalized tooth. A diagnosis of perennial allergic rhinitis was made. The affected tooth was later removed by a local dentist. X-ray examination of the paranasal sinuses was negative. The patient returned to the Clinic about a year later with no improvement of symptoms and was referred to the Department of Allergy where she was found to react to household dust and inhalants. She was started on a course of desensitization injections which she voluntarily discontinued after a short period. We subsequently performed an adenoidectomy but this procedure also failed to offer relief. The patient was next seen 7 years later with a chief complaint of deafness which had occurred 7 weeks previously. A diagnosis of otosclerosis was made. Her nasal symptoms were still present. She was examined 3 months later at which time she gave a 3 weeks' history of serosanguineous discharge from the right nasal fossa. Nasal examination revealed bilateral ulceration on the basilar septal ridges.

Blood studies revealed 4,600,000 red cells with a hemoglobin concentration of 12.5 Gm. per cent; 9,950 leukocytes per cu. mm. with normal differential proportions. The serology was negative and blood sugar was well within normal limits. Smears and culture of the nasal lesion revealed colon bacillus and Staphylococcus albus. Sulfathiazole ointment, penicillin, and aureomycin were ineffectual, although Gantrisin seemed to improve the lesions.

Subsequently the patient suffered a relapse and was observed elsewhere. She was given nicotinic acid and experienced a rather long period of remission on this therapy. A few months later, however, the septal lesions recurred actively. She was given cortisone which resulted in almost immediate amelioration and apparent cure. Within several months, following discontinuance of this agent, the ulcerations again returned. She is once more receiving cortisone, but the general course of the disease has been one of deterioration.

We have observed an additional case in a 49-year-old white man who presents an unusual history of alternate ulcerative involvement of the right and left lateral pharyngeal walls. The ulcerations have been undergoing spontaneous remissions following unilateral involvement lasting several months, only to result in a breakdown of the same or opposite wall. His relapses have been recurring with increasing frequency and violence. The ulcers are shallow and

extend from the lower lateral nasopharynx to the vallecula and aryepiglottic fold, involving the ipsilateral half of the epiglottis. The ulcers are covered with a white pseudomembrane. Pain is present but not particularly aggravating. As a result of the repeated ulcerative episodes about 70 per cent of the epiglottis has been eroded. Biopsies of the lesions have been inconclusive on microscopic examination and diagnosed as "chronic granulomatous inflammation." His general condition has been one of gradual deterioration. After the failure of several forms of therapy, he has recently been given a course of cortisone with a partial remission. A small area behind the right posterior pillar still persists following several weeks of treatment with this agent. Because of the atypical nature we have not included this with the case reports. We believe, however, that it probably represents an instance of idiopathic lethal granulomatous ulceration involving only the pharynx and larynx.

The ultimate roles of cortisone and ACTH in the treatment of idiopathic lethal granulomatous ulceration of the nose and face must be more fully evaluated. To date this corticoid of the adrenal gland and the stimulating hormone yielded by the anterior lobe of the pituitary gland appear to offer the only effective remedial agents available to the clinician. Our brief experience with these agents, however, indicates that, though improvement may occur, a cure probably cannot be obtained even with these forms of therapy. Whether repeated courses can adequately control the lesions so that the patient may have a normal life span must be determined. Since all previous therapeutic approaches have failed to result in a cure of this unusual disorder, the prognosis should be regarded with extreme pessimism and, until the nature has been established, the treatment must, of necessity, be empirical.

Summary

The clinical features of idiopathic lethal granulomatous ulceration of the nose and face have been described; the etiology remains undetermined notwithstanding exhaustive diagnostic efforts to isolate a causative agent. Six cases which we have observed during the past 15 years have been reported. Three of these have terminated fatally; 2 patients are in a state of deterioration, and one with whom we lost contact was reported as well and symptom-free. Therapy has been discussed briefly. Cortisone and ACTH appear to be the only therapeutic agents of value at the present time and, since they may effect only temporary remission of the lesions, their significance has yet to be fully assessed. It is our impression that a therapeutic agent for effective cure remains to be discovered and, as other authors have pointed out, much investigative work must be done in establishing the etiology of this affliction.

References

1. Williams, H. L.: Lethal granulomatous ulceration involving midline facial tissues. Ann. Otol., Rhin., and Laryng. **58**:1013 (Dec.) 1949.
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References

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2. Hoover, W. B.: Granulomatous ulcer of nose and face of unknown cause, usually progressive, gangrenous and fatal. Arch. Otolaryng. **34**:865 (Nov.) 1941.

3. Isbell, D.: Chronic granulomatous ulcer of nose of unknown cause. Ann. Otol., Rhin., and Laryng. **52**:501 (June) 1943.

4. Lierle, D. M.: Chronic infectious granuloma of nose. Arch. Otolaryng. **36**:940 (Dec.) 1942.

5. Lewy, A.: Case of gangrenous osteomyelitis of paranasal sinuses. Arch. Otolaryng. **27**:91 (Jan.) 1938.

6. Stewart, J. P.: Progressive lethal granulomatous ulceration of nose. J. Laryng. and Otol. **48**:657 (Oct.) 1933.

7. Woods, R.: Malignant granuloma of nose. Brit. M. J. **2**:65 (July 16) 1921.

8. Wood, G. B.: Case of multilating granuloma of nose and face with fatal ending. Tr. Am. Laryng. A. **53**:63, 1931.

THE DIAGNOSTIC VALUE OF CAROTID ARTERIOGRAPHY

A Preliminary Report

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CEREBRAL angiography is now almost universally recognized as a valuable addition to the diagnostic armamentarium of the neurologic surgeon. A clearly defined picture of the vessels of the brain, whether normal or abnormal, is most useful in helping the surgeon decide in favor of or against an intracranial operation. This is especially true in cases of vascular malformations, aneurysms, thromboses of the venous sinuses, and other lesions which do not cause displacement or distortion of the ventricular system.

The feasibility of injecting a radio-opaque medium into the arteries supplying the brain and its coverings, with a view to outlining the intracranial vessels by x-rays, was demonstrated by Egas Moniz,[1] a Portuguese neurosurgeon, in 1927. Since his original description, the methods and materials utilized have varied considerably. All modifications have been made with the intention of obtaining clearer and more diagnostic pictures, with a minimum of risk to the patient.

Many elaborate technics have been developed in order to obtain certain specific views of the cerebral circulation; these have recently included the use of the x-ray motion picture camera. However, it is unnecessary to use complicated equipment in taking cerebral angiograms. Usually only single posteroanterior and lateral views are required to establish the presence or absence of the suspected lesion. Variations in the timing of the exposures may be helpful, as the arterial, capillary and venous phases of the circulation may be photographed at will.

Injection of one vertebral artery will outline the vessels in the posterior fossa bilaterally if the circulation is normal, including also the posterior communicating arteries in some patients. Injection of the internal carotid artery in the neck causes filling of the anterior and middle cerebral circulations on the same side, often showing the posterior communicating and posterior cerebral groups as well. Variations in the over-all picture may occur; i. e., both anterior cerebral arteries may fill from a single injection. Both the internal carotid and vertebral arteries may be approached and injected by either open operation or a percutaneous route.

Moniz, in his original description of carotid arteriography, described the open technic in which the internal carotid artery was exposed in the neck by operation, and radio-opaque material was injected under direct vision. He used two media for injection, 30 per cent strontium bromide and 25 per cent

sodium iodide,[1] in volumes varying from 6 to 15 cc. Common complications of these injections, carried out under local anesthesia, were the initiation of convulsions, and frequent delayed reactions to the bromide or iodide. Davies[2] subsequently observed that sodium iodide was a dangerous substance to inject into atheromatous vessels.

In 1933, Moniz[3,4] described the use of thorium dioxide (thorotrast) in volumes of 10 to 16 cc. as a more suitable medium for injection. The larger quantity was injected when it was desired to outline the venous phase of the circulation. Many workers[5,6,7] have used thorotrast since the original report, and there are various descriptions of its toxic effects. Because of the slight degree of radioactivity exhibited by the salt, the danger of damage to the reticulo-endothelial system must be considered, a point stressed by Davis[2] in 1937. At the same time he indicated that the volume injected in cerebral angiography is considerably less than the 60 to 70 cc. used to outline the spleen radiographically. In 1942 King[8] reported enthusiastically on the use of thorotrast, and detected no permanent toxic side effects when the total volume injected was maintained below 25 cc. Linden[7] described the use of thorotrast arteriography in diagnosing three intracranial aneurysms in 1936, and List and Hodges[9] referred to it in the diagnosis of intracranial expanding lesions.

Thorotrast is not the ideal contrast medium to use in cerebral arteriography; its ill effects have been described as ranging from transient rashes through temporary hemiplegia and convulsions, to liver damage and possible sarcogenesis. This latter complication was discussed by Ingraham and Cobb[10] in 1947.

Although thorotrast is still used, diodrast, an organic iodine compound introduced into the literature by Shimidzu[11] in 1937, appears to be a safer medium. Shimidzu probably was the first to use the closed or percutaneous technic for approaching the internal carotid artery. He had utilized the method since 1932, having injected such media as thorotrast, uroselectan β and parabrodil.

Apparently the first direct recommendation for the use of diodrast was made in 1939 by Gross,[12] who used the open technic for injecting the dye into dogs and humans. He observed a transient cutaneous flush, sweating, and an elevation of the systolic blood pressure following each injection.

The use of radio-opaque substances other than thorotrast and diodrast has been generally discontinued. While the radio-opacity of diodrast in the usual 35 per cent concentration is significantly less than that of thorotrast, this disadvantage is counteracted by the decreased danger of toxic side reactions.

Anesthesia is an important factor in the making of good arteriograms. The sudden injection of a radio-opaque dye into the internal carotid artery, under local anesthesia, causes the patient to experience a sudden surge of pain in the corresponding side of the head. This has been described by one of our patients who underwent the examination elsewhere, as "like the flame of a blowtorch." Such severe discomfort may cause movement, thereby ruining an x-ray picture. Even under light pentothal anesthesia a patient will react by generalized muscular spasm after each injection, and move his head if not

restrained. General anesthesia is preferred as it is more comfortable for the patient and more conducive to satisfactory radiography.

More than 700 arteriograms have been made at the Cleveland Clinic since June 25, 1946, the vast majority by the percutaneous method, under sodium pentothal anesthesia using diodrast as the contrast medium. Both the internal carotid and the vertebral arteries have been injected and, since the first few cases, the closed route has been used exclusively. Thirty-five per cent diodrast is utilized as the routine dye, 10 cc. for the lateral pictures and 10 to 12 cc. for the posteroanterior view. Injection is made as rapidly as possible through an 18 gage needle from a 10 cc. syringe. The artery is entered with the patient under light pentothal anesthesia, and 30 to 60 seconds before the injection an additional quantity of 2 or 3 cc. of pentothal is administered to prevent movement during exposure of the film. The posteroanterior view is preferable to the anteroposterior, because of the increased clarity of visualization of the anterior portion of the anterior cerebral artery.

This report concerns 145 patients who underwent internal carotid arteriography. All cases were investigated in the early days of arteriography at the Cleveland Clinic, and include the majority subjected to the open operation. They represent a small unselected portion of the entire series of patients, on whom a further report will be made at a later date.

Complications in this small group have been minimal. No instances of postoperative convulsions, iodine sensitivity or other serious conditions have been recorded. In the early days occasional anxiety developed concerning the size of some of the hematomata which formed after withdrawal of the needle. However, evacuation of clots has never been necessary to relieve obstruction to the patients' airway, and hematoma formation can always be minimized by prolonged digital pressure over the site of puncture. Diodrast, if injected into the tissues of the neck outside the vessels, is rapidly absorbed and apparently causes no permanent sequelae. The postoperative morbidity has also been minimal, and patients demonstrating negative arteriograms usually are allowed to go home on the day following the procedure.

We believe that the absence of serious complications in our patients has been largely due to the use of sodium pentothal as the anesthetic agent.

Although we are relying more and more on arteriography in the diagnosis of intracranial lesions, we do not hesitate to follow the procedure by air studies if the arteriograms are not completely conclusive. We feel, however, that a positive arteriogram frequently gives a more accurate localization than do the air contrast pictures. Also whenever possible, we prefer to avoid the more traumatic procedures of encephalography or ventriculography.

Table 1

Cases reviewed	145
Open arteriograms	23
Age oldest patient	71
Age youngest patient	6 months

Table 2

(A) Diagnostic of site of lesion	68
(B) Diagnostic of type of lesion, i.e., tumor, aneurysm, etc.	62
(C) Confirmatory of no lesion deforming the blood vessels, i.e., tic douloureux, idiopathic convulsions, cerebral atrophy, etc.	37
(D) Total arteriograms confirming preoperative diagnosis (A) and (C)	105

Of the 68 arteriograms showing definite intracranial lesions, 62 also accurately localized the position. The 37 represented in table 2 (C) are considered as positive results because they confirmed a clinical impression of no space-occupying lesions.

Twenty-eight of the 68 positively identified lesions caused deformities or displacements of the ventricular system and could have been diagnosed conceivably by air contrast studies. This left a total of 40 lesions, 27.6 per cent of the entire series, which could not have been definitely diagnosed preoperatively.

A detailed breakdown of these 40 cases follow:

Type:	(a) aneurysms	24
	(b) arteriovenous malformations	11
	(c) hemangioma	1
	(d) internal carotid occlusions	1
	(e) absence or occlusion of right anterior cerebral artery	1
	(f) other vascular anomalies	2
	Total	40

One case with a negative carotid arteriogram was found at surgery to have an arteriovenous malformation at the cerebellopontine angle.

Summary

1. Internal carotid arteriography using 35 per cent diodrast, under sodium pentothal anesthesia, is a safe procedure with minimal complications.

2. In the present series of 145 cases, internal carotid arteriography increased the percentage of positive preoperative diagnoses by 27.6 per cent over that obtained by other diagnostic measures alone.

References

1. Egas Moniz: Arterial encephalography, its importance in localization of cerebral tumors. Rev. neurol. **2**:72 (July) 1927.
2. Davies, H.: Cerebral arteriography. Brit. J. Radiol. **10**:871 (Dec.) 1937.

3. Egas Moniz: Cerebral angiography with thorotrast. Arch. Neurol. and Psychiat. **29**:1318 (June) 1933.

4. Egas Moniz: Cerebral angiography. Lancet **2**:1144 (Nov. 18) 1933.

5. Hodes, P. J., Perryman, C. R. and Chamberlain, R. H.: Cerebral angiography. Am. J. Roentgenol. **58**:543 (Nov.) 1947.

6. Loman, J. and Myerson, A.: Visualization of cerebral vessels by direct intracarotid injection of thorium dioxide. Am. J. Roentgenol. **35**:188 (Feb.) 1936.

7. Linden, L. C. E.: Cerebral arteriography. M. J. Australia **1**:849, 1936.

8. King, A. B.: Demonstration of basilar artery and its branches with thorotrast. Bull. Johns Hopkins Hosp. **70**:81 (Jan.) 1942.

9. List, C. F. and Hodges, F. J.: Angiographic diagnosis of expanding intracranial lesions by vascular displacement. Radiology **47**:319 (Oct.) 1946.

10. Ingraham, F. D. and Cobb, C. A., Jr.: Cerebral angiography: Technique using dilute diodrast. J. Neurosurg. **4**:422 (Sept.) 1947.

11. Shimidzu, K.: Beitrage zur Arteriographie des Gehirns—einfache percutane Methode. Arch. f. klin. Chir. **188**:295, 1937.

12. Gross, S. W.: Cerebral arteriography in dog and in man with a rapidly excreted organic iodide. Proc. Soc. Exper. Biol. and Med. **42**:258 (Oct.) 1939.

SPONTANEOUS INTERNAL BILIARY FISTULA

A Case of Cholecystocolic Fistula

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RECENTLY we had occasion to make the preoperative diagnosis of cholecystocolic fistula and demonstrate this complication of gallbladder disease at operation. The symptoms and roentgen findings were of sufficient diagnostic interest to stimulate this report.

The patient had a history of multiple attacks of acute cholecystitis for many years and apparently developed the cholecystocolic fistula a few weeks before its recognition. The onset of fistula formation was characterized by a period of upper abdominal pain, fever, prostration, and diarrhea. Barium x-ray study of the colon was diagnostic for an internal biliary fistula.

Case Report

A widow, aged 73, was admitted to the Clinic hospital with a presumptive diagnosis of subsiding acute cholecystitis. Twenty-three years previously a clinical diagnosis of chronic cholecystitis had been made because of a history of recurrent attacks of pain in the right upper abdomen radiating into the right scapular region, often accompanied by nausea and vomiting. The gallbladder had been normal on subsequent repeated cholecystograms until one year prior to admission when gallstones were demonstrated for the first time.

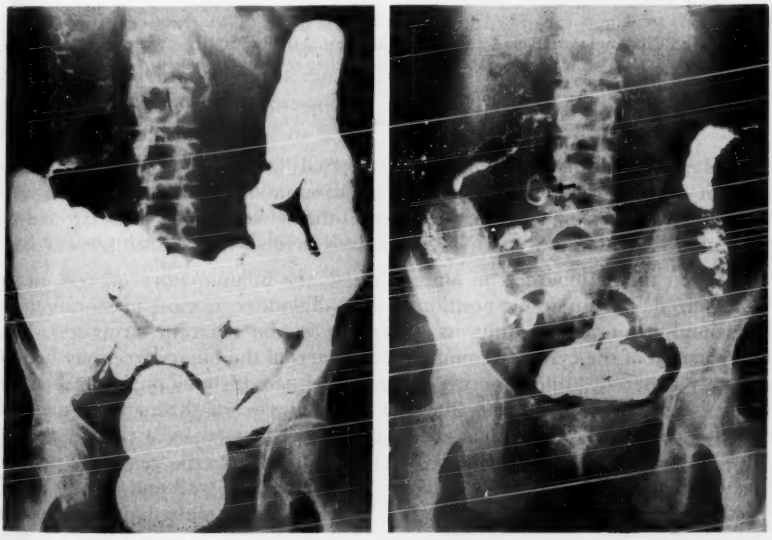
Three weeks before hospital admission the patient experienced a recurrent dull ache in the epigastrium which became progressively intense. She developed a fever ranging from 100 to 102 F. which lasted 5 to 6 days, and passed numerous foul green loose stools. The patient entered a community hospital and during the period of observation was unable to tolerate food. There was no jaundice, no acholic stools or dark urine. She was discharged after the fever subsided and one week later was admitted to the Cleveland Clinic Hospital.

Physical examination revealed an elderly, thin woman who appeared chronically ill. A few rales were evident in the right lung field which cleared with coughing. The liver was moderately tender, enlarged to the level of the right iliac crest and below the umbilicus in the midline; there was also a tender mass in the left periumbilical region which descended with the liver on deep inspiration. Proctoscopic examination revealed multiple small rectal polyps which appeared benign. A needle biopsy of the liver was reported as hemochromatosis. Streptococcus faecalis was isolated on urine culture, and cystoscopy demonstrated a diffuse moderate cystitis with a negative retrograde pyelogram.

The patient was placed on Mandelamine with prompt disappearance of all urinary symptoms. X-ray of the colon several days later revealed polypoid changes in the sigmoid colon which were interpreted as a probable neoplasm. In addition there was a fistulous communication between the biliary tree and the hepatic flexure (figs. 1a

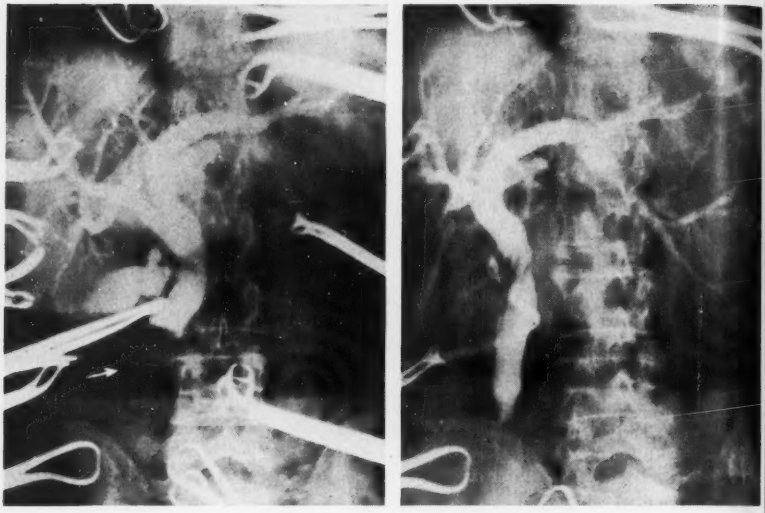
and b). The common duct was dilated and the large calculus was suspected of having caused common duct obstruction. As presence of a sigmoid tumor would require immediate attention, the patient was explored through a left lower rectus incision. However, careful examination of the entire left colon failed to reveal evidence of tumor despite the previous x-ray findings; the right upper abdomen disclosed numerous adhesions. The gallbladder was filled with palpable stones and was densely adherent to the right transverse colon. The abdomen was closed and 11 days later the patient was explored through a right midabdominal incision and the cholecystocolic fistula was demonstrated. Two faceted stones in the dilated common duct were removed after division of the fistulous tract and cholecystectomy. A cholangiogram (fig. 2a) made at the time of surgery, shows the dilated common duct and the obstructing calculi. The accompanying cholangiogram (fig. 2b) was made after removal of the calculi. Drainage of the common duct was provided by means of a T tube. The fistulous opening in the right transverse colon was closed with a standard two layer suture technic.

The patient's postoperative course was uneventful and the T tube in the common duct was removed on the sixth postoperative day. Pathologic examination revealed the gallbladder as the site of severe acute and chronic cholecystitis; it contained five faceted stones approximately 1.5 cm. in diameter which were similar to the two calculi removed from the common duct. The cholecystocolic fistula communicated with the fundus of the gallbladder. Nine months later the patient was free from complaints relating to the gastrointestinal tract or abdomen.



(a) (b)

FIG. 1. (a) Barium and gas outlining fistulous communication between bilary tree and hepatic flexure of colon. (b) Barium outlining common duct stone (arrow) right of fourth lumbar interspace.



(a) (b)

FIG. 2. (a) Cholangiogram made at time of surgery showing dilated common duct and obstructing calculi (arrow). (b) After removal of calculi.

Etiology

The recognition of spontaneous internal biliary fistulas is uncommon except during surgery or at postmortem examination. The presence of fistulous connections between the bilary tract and other viscera is not unusual, and the commonest of these internal biliary fistulas involve the gastrointestinal tract.

When the gallbladder becomes infected, the inflammatory process usually is localized. The anatomic position of the gallbladder, in close proximity to the surrounding organs, permits its adherence to the adjacent structures. With obstruction of the cystic or common duct, parts of the biliary tree may become densely adherent to neighboring organs; local necrosis may occur, and a stone may be discharged into the intestine or other viscera through the acquired spontaneous fistulous opening. Fistulas may be formed by a second process, i. e. subsequent to rupture of a diseased gallbladder; the resultant pericholecystic abscess may produce necrosis of the intestinal wall and form a fistula, with the abscess cavity providing the tract. Finally, malignant neoplasm or peptic ulcer may initiate a perforation with concomitant fistula formation.

The reflex of gastric or intestinal contents into the biliary tree often produces an extensive cholangitis. Extensive cirrhosis of the liver can result from retrograde infections[1,2] inducing unusual gastrointestinal symptoms. Most biliary fistulas are single; multiple fistulas are rare.

Incidence

Occurrences of internal biliary fistulas have been reported between any part of the biliary tract and adjacent parts of neighboring organs. Kehr[3] found 100 such fistulas in 2000 routine cholecystectomies; Bernhard[4] demonstrated 109 fistulas in 6,263 biliary operations, and Puestow[5] found 16 fistulas in 500 operations for biliary abnormalities. Hicken and Coray[6] estimated that 4 per cent of all patients requiring surgery for biliary disease have internal biliary fistula.

In 30,000 autopsies, Borman and Rigler[7] found 67 internal biliary fistulas and, in 10,866 autopsies reported by Roth et al,[8] there were 43 internal biliary fistulas.

Most frequently the fistula appears between the gallbladder and the duodenum. The secondary site of occurrence is between the bile ducts and duodenum. Fistulas between the biliary system and the colon, stomach, or other adjacent organs are observed less frequently.

Garland and Brown[9] reported 5 cases of internal biliary fistulas diagnosed preoperatively by x-ray examinations, and summarized the previously reported cases. Of the 90 cases reviewed, 46 were cholecystoduodenal fistulas, 24 choledochoduodenal fistulas, and 10 cholecystocolic fistulas; in 4 the anatomic locations were not determined. Of the remaining 6 cases, 3 were cholecystogastric fistulas, one was a cholecystoduodenocolic fistula, one a choledochogastric fistula, and one a choledochocolic fistula. The presence of an internal biliary fistula does not necessarily imply poor health. McQueeney[10] reported 2 patients having cholecystoduodenal fistulas who enjoyed normal health; in one case the fistula had existed for 19 years, and in the other the fistula had been present for 15 years.

The gastrointestinal viscera, however, are not the only organs violated by spontaneous biliary fistulas. Gallstones have been passed in the urine, and observed in the placenta after labor. Occasionally, even the precordial or pleural cavities are invaded by the contents of a diseased gallbladder. Dean[11] reports that gallstones have been found plugging the portal vein and hepatic artery.

Diagnosis

The preoperative diagnosis and localization of internal biliary fistulas depend almost entirely upon x-ray examination. Clinical examination rarely suggests biliary fistula unless the patient has a history of having passed gallstones in the stool. Many cases are demonstrated accidentally at the time of operation and any symptoms produced by the fistulous tract usually have been overshadowed by those of gallbladder disease. In recent years preoperative diagnoses have been made more frequently with the increased utilization of roentgen studies in biliary disease and the establishment of criteria for the identification of these fistulas. The most common circumstance is the so-called "gallstone ileus," where acute obstruction of the small intestine is produced by a gallstone. X-ray recognition rests upon the characteristic picture of small

bowel obstruction together with either gas in the biliary tree or a radio-opaque gallstone at the tip of a dilated loop of bowel.

Hunt and Herbst[12] reported the first case diagnosed by x-ray in 1915, and in a series of 153 cases reported by Judd and Burden[13] in 1925 only one case was diagnosed preoperatively. In 1937 Borman and Rigler[7] recognized 86 fistulas preoperatively out of 267 cases.

The positive diagnosis of biliary fistula can be established when barium outlines the tract or portions of the biliary tree, either by oral administration or by means of an enema (figs. 1a and b). Corroborative x-ray findings include the presence of air or residual barium in the biliary tract, nonvisualization of the gallbladder on cholecystography, and changes in the mucous membranes of parts such as the duodenum and colon at the site of the fistula.

Barium x-ray of the colon is the most positive means of making the correct diagnosis of biliary colic fistulas, and air contrast studies are second in reliability. The presence of air in the biliary system, especially the interlobar ducts of the liver, is almost always diagnostic of some abnormal communication between the biliary and digestive systems. Occasionally bacilli infecting the gallbladder will produce enough gas to outline the biliary system, and gas has been known to reflux through the ampulla of Vater into the common duct outlining the bile ducts.

Symptoms

Weight loss, jaundice, and diarrhea are common symptoms in biliary tract fistula but are not pathognomonic. The weight loss is usually secondary to the diarrhea and the amount of liver damage present. Jaundice is generally due to associated cholangitis and hepatitis resulting from an ascending infection by intestinal organisms. Puestow[5] reported high virulence and acute hepatic infection most prominent in the cases of cholecystocolic fistula; he attributed these to the high bacterial flora count of the colon. Diarrhea is most pronounced in the cholecystocolic fistulas associated with a large tract which permits the full laxative effect of bile to act directly in the colon through the fistula. Most patients feel improved or well after the fistula forms as this permits the inflammatory debris or calculi to be drained spontaneously and to be carried away with the intestinal contents. The formation of a communication between the biliary tree and the gastrointestinal tract may sometimes be a life-saving accident with resultant spontaneous internal drainage.

Operative Treatment

The presence of an internal biliary fistula increases the risk of surgical intervention many times over that of uncomplicated biliary tract disease. However, a large fistula may so disable a patient that surgical intervention is indicated despite the increased operative risk. Spontaneous closure with permanent remission is rare in these cases.

In order to prevent the formation of bilary fistula the gallbladder and all calculi should be removed in the early stages of biliary tract disease. If oper-

ation is not delayed the massive adhesions and inflammatory reaction which usually accompany such formation may be avoided; these complications increase the technical difficulties of the procedure. Early surgery for cholecystolithiasis would circumvent the possible perforation of the gallbladder at a later date and the resultant high mortality. If the fistula is unrecognized or if the lumen is small at the time of operation, the surgeon may excise the fistula and inadvertently overlook an opening in the bowel. Such an oversight can result in peritonitis. Large fistulous openings or cavities, in these cases, should be drained in the manner of any other intraabdominal abscess after correction of the underlying cause.

Summary

A case of cholecystocolic fistula has been presented and the pertinent data associated with internal biliary fistulas briefly reviewed. An accurate preoperative diagnosis of cholecystocolic fistula was made by means of a barium x-ray study of the colon and confirmed at operation. This complication of gallbladder disease can be avoided by early removal of the seriously diseased gallbladder.

References

1. Jenkinson, D. L. and Lowry, H. M.: Cholecystocolic fistula diagnosed by roentgen examination; case report and review. Am. J. Roentgenol. **60**:658 (Nov.) 1948.
2. Lovell, D. L.: Internal biliary fistulas; report of case. South. Surgeon **13**:152 (Feb.) 1947.
3. Kehr: cited by Puestow.[5]
4. Bernhard, F.: Die Fruh- und Spatergebnisse der Cholecystogastrostomie, der Cholecystoduodeno- und Choledochoduodenostomie bei 128 Fallen. Ztschr. f. Chir. **242**:736, 1934.
5. Puestow, C. B.: Spontaneous internal biliary fistula. Ann. Surg. **115**:1043 (June) 1942.
6. Hicken, N. F. and Coray, Q. B.: Spontaneous gastrointestinal biliary fistulas. Surg., Gynec. and Obst. **82**:723 (June) 1946.
7. Borman, C. N. and Rigler, L. G.: Spontaneous internal biliary fistula and gallstone obstruction, with particular reference to roentgenologic diagnosis. Surgery **1**:349 (March) 1937.
8. Roth, Schroeder and Schloth: cited by Judd.[13]
9. Garland, L. H. and Brown, J. M.: Roentgen diagnosis of spontaneous internal biliary fistulae, especially those involving the common bile duct. Radiology **38**:154 (Feb.) 1942.
10. McQueeney, A. M.: Internal biliary fistulae and intestinal obstruction due to gallstones. Ann. Surg. **110**:50 (July) 1939.
11. Dean, G. O.: Internal biliary fistulas; discussion of internal biliary fistulas based on 29 cases. Surgery **5**:857 (June) 1939.
12. Hunt and Herbst: cited by Jenkinson and Lowry.[1]
13. Judd, E. S. and Burden, V. G.: Internal biliary fistula. Ann. Surg. **81**:305 (Jan.) 1925.

HORMONE THERAPY IN MALIGNANCIES

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HORMONE therapy in the treatment of cancer is useful for two purposes: (1) as a palliative in incurable cases; (2) for study of the behavior of cancer in an attempt to understand its natural history. It is never curative and for that reason should not be depended upon when surgical removal of the primary lesion can be accomplished before metastases have occurred. There are perhaps some exceptions to this rule; for example, as a therapeutic measure for patients severely ill with some other incurable ailment or in the aged patient whose life expectancy is limited. This therapy may be dangerous if misused. Its action is not well understood. Even though cures are not produced it may, nevertheless, relieve pain, improve health temporarily, and prolong life in some patients.

Hormonal therapy may be regarded solely as hormonal administration or it may be accepted as indicating manipulation or withdrawal of existing hormones in some cases. We shall consider both aspects briefly in relation to breast and prostatic cancer.

Castration and Cancer of the Breast in Women

As early as 1886, Sir George Beatson[1] recommended oophorectomy as a treatment for cancer of the female breast. Adair[2] has recently estimated that it is useful in 15 to 30 per cent of patients with recurrent or metastatic disease. Little or no response is to be found in lymph gland metastases or in the primary tumor. X-ray castration may be capable of causing definite regression in pulmonary metastases temporarily. A good result brings relief from pain, increase in appetite and weight, regression of bone metastases and, occasionally, pulmonary metastases. Although always transient, desirable effects may persist for a year.

Castration of men for cancer of the male breast is often followed by good results.[3,4,5,6,7] It is claimed that such effects are even more striking than for carcinoma of the prostate. Interestingly, in contrast to women who are more likely to obtain the best results in younger years, men are more often benefited by this treatment if they are over 60.

Administration of Estrogens for Breast Cancer

Haddow,[8] in 1944, used trichlorphenyl ethylene, triphenyl methyl ethylene and stilbestrol in 73 patients with breast cancer. With the first compound there were good responses in 10 of 22 patients treated and, with stilbestrol, improvement in 5 of 14 treated, or approximately half of the patients in each group.

In 1944, 10 British observers[9] reported their results with estrogens in the treatment of 168 cases of mammary cancer. The most striking fact arising from the study was that the response proved vastly superior in women over 60 years of age. This observation is supported by the most recent report of the Therapeutic Trials Committee's Subcommittee on steroids.[10]

My observations regarding the use of steroids[11] in the treatment of breast cancer are based on the results of many investigators among whom are Adair,[2] Farrow,[3] Nathanson,[12,13] Huggins,[14] and Vest[15] in this country, and Haddow,[8] Fergusson[16] and others in England. In addition, I have relied upon the most recent report on the subject for many of my statistics. This is the third analysis of all cases treated by participating investigators under the direction of the Subcommittee on Steroids and Cancer of the American Medical Association. The data were analyzed under the supervision of Dr. Walton Van Winkle October 27, 1950.

Regarding the Choice of Estrogen

Stilbestrol has been used extensively and, in general, is more practical because it is effective orally and is inexpensive. In addition, there is little to suggest the superiority of any other estrogen. Among 695 patients treated with various steroids, it appeared that ethinyl estradiol had a better effect in causing regression of soft tissue lesions; even here it is not certain that its advantage of 67 per cent compared to 53 per cent for stilbestrol would not have been less obvious had dosages been equalized.

An attempt has been made to determine the optimum dose. With stilbestrol, subjective improvement is much greater after the total dose has reached 2.0 Gm. than with lower doses. Objective changes in the primary lesion, soft tissue and bony lesions require larger total doses. In these cases good results are about doubled when the dose rises over 4.0 Gm. total. It is obvious that, when the commoner dose of 15 mg. per day is used, it takes 4 months to reach 2.0 Gm. and 8 months to reach 4.0 Gm. Patients treated for more than 6 months have, on the whole, done decidedly better than those treated for a lesser interval. Here again it is difficult to know whether the amount of the drug is the important factor or whether, for example, patients with milder disease live longer independent of treatment. The facts suggest that doses as large as 30 mg. per day or more are worthy of a trial.

In considering estrogen therapy for cancer of the breast (table 1) age is such an important factor that it is useless to consider treatment in a patient under 50 years of age, skeletal lesions being of the utmost consequence. No example of improvement in skeletal metastasis has been seen following estrogen therapy in a premenopausal woman. Before the menopause, estrogen has no advantage over androgens in controlling soft tissue lesions which are greatly influenced in about 23 per cent of patients by either testosterone or stilbestrol. However, after the menopause conditions change, primary and other soft tissue lesions respond much better to estrogens than to androgens.

Regression or healing of bone metastases is obvious after androgens in only

Table 1

REGRESSION OF BONE LESIONS COMPARED TO SOFT TISSUE LESIONS BEFORE AND AFTER MENOPAUSE

Preparation	Bone Lesions		Soft Tissue Lesions	
	Per Cent Premen.	Regression Postmen.	Per Cent Premen.	Regression Postmen.
Testosterone propionate	10%	14%	24%	22%
Diethylstilbestrol		14%	22%	53%
Ethinyl estradiol		10%		67%
Premarin		16%		44%

Table 2

RELATION OF AGE TO SURVIVAL IN BREAST CANCER

Mean Time from Admission to Death		
Age	Estrogen	Testosterone
20 - 29		9.0
30 - 39	10.0	8.5
40 - 49	7.6	7.5
50 - 59	9.7	9.2
60 - 69	9.1	9.3
70 - 79	10.6	7.4
80 - 89	12.3	
Mean	9.8 mos.	8.5 mos.

10 per cent of premenopausal patients and subsequent to androgen or estrogen therapy in about 15 per cent of patients having experienced the menopause.

One of the most striking clinical changes is the healing of large ulcerating carcinomata. In some patients the healing is complete with epithelialization and a contracture of tissue suggesting cicatrix formation. Almost complete disappearance of lung metastases, according to x-ray, may be demonstrated following estrogen therapy. In some, surprisingly, improvement continues many months after cessation of treatment even though little change had been evident during therapy (fig. 1a and b).

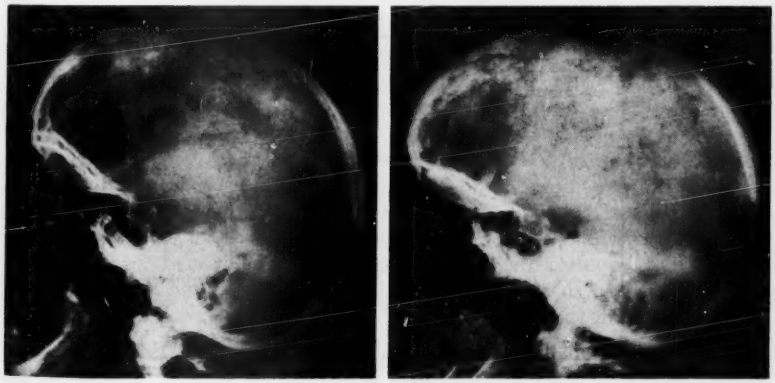
The individual response is difficult if not impossible to predict, and apparently is not related closely to the type of carcinoma present.

Life expectancy varies greatly after initiation of therapy. With estrogens, it relates to the age of the patient, the older person having a greater period of survival; with testosterone this is not apparent (table 2).

A year's survival time is considered to be a reasonable estimate, although some patients live 25 months or longer. Interestingly, the persons who have survived the longest are those with lung metastases which have regressed.

Common untoward effects of stilbestrol, some of which may at times interfere with its use, are listed in table 3 together with the approximate frequencies of occurrence. Despite preconceived opinion, further studies have shown that the various estrogens differ little in these respects.

Hypercalcemia occurs with estrogen therapy less frequently than with androgen therapy. Serum calcium levels should be determined in any patient for whom steroid hormone therapy is indicated, as hypercalcemia may appear or increase or, in some cases, diminish and disappear during therapy (graphs 1 and 2). As the calcium falls alkaline phosphatase may rise, indicating bone healing. It may be suspected clinically if nausea, vomiting, headache, or



(a) (b)

FIG. 1. (a) Metastases to skull from carcinoma of breast following methyl testosterone, 300 mg. three times a week for 18 months, plus stilbestrol, 15 mg. daily for 3 months. (b) Striking diminution in metastases 6 months after withdrawal of steroid therapy.

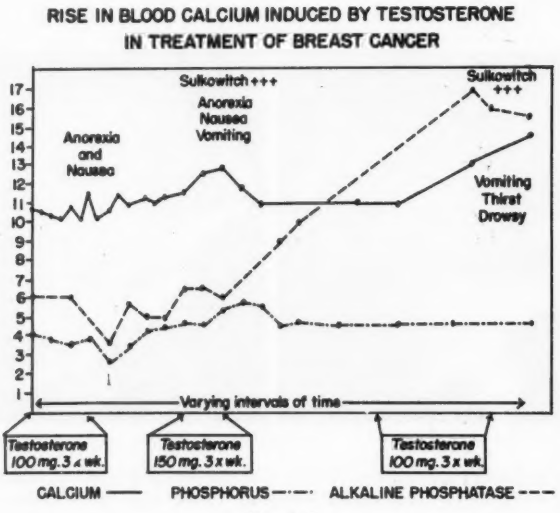
polyuria are present. It is aggravated by skeletal immobilization during severe pain, and lessened when activity is permissible due to relief of pain. It is usually associated with bony metastases but may occur in cases in which no skeletal lesions are evident. Unlike the hypercalcemia of hyperparathyroidism or vitamin D intoxication, serum calcium may reach levels as high as 20 or more with no ascribable symptoms.

Estrogen is utilized primarily for inoperable breast cancer in postmenopausal women with soft tissue or lung metastases. There is little difference in the effectiveness of various estrogens; however ethinyl estradiol may be slightly superior. A minimum of 4 Gm. should be prescribed over a period of 6 months.

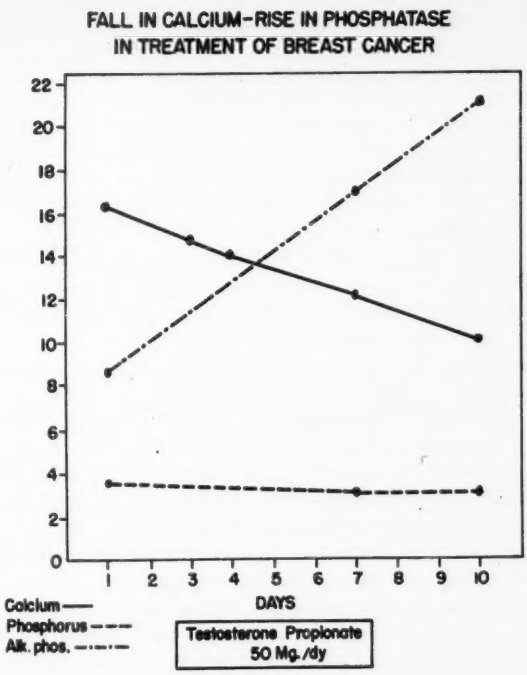
Administration of Androgens for Breast Cancer

In general, androgens have been found more useful than estrogens in the treatment of bony lesions, although soft tissue lesions are sometimes significantly benefited by androgens. As with estrogens, the result to be expected in a given patient is impossible to predict. Symptomatic response is frequently dramatic, and pain severe enough to require morphine has been almost completely relieved within 2 days in some patients. In others, persistent use of testosterone may not be followed by a good response until the hormone has been continued for 8 to 10 weeks. It is also interesting that in some instances improvement may continue for months after withdrawal of the drug.

Among the most impressive changes following testosterone therapy is the alteration in roentgen appearance of skeletal metastases. The pain may disappear with no visible change in the lesions, or the demineralized area may



Graph 1



Graph 2

become dense; even more exceptional are signs suggestive of healing in some lesions and of progression in adjacent ones. Occasionally, the entire process appears to progress with increased vigor under therapy. In some elderly patients soft tissue lesions and lung metastases may regress definitely during testosterone therapy.

During therapy, it is suggested that the levels of alkaline phosphatase in the blood be checked accurately. An increase of three to five times the original level may be seen which indicates healing of the lesions. The serum calcium should always be measured before beginning therapy and, if it is noticeably increased, treatment should be withheld or given with caution. Hypercalcemia during therapy has been found in about 10 per cent of testosterone-treated patients as compared to 3 per cent of those under estrogen therapy.

The subjective response to androgens in premenopausal women is distinctly greater than with estrogens. This is often an important consideration; even though a woman may not live longer or have a more definite objective improvement, nevertheless the androgens may give a sense of vigor and well-being which add greatly to her comfort during the months she does live.

Table 4 demonstrates the relative value of estrogens and androgens in

bringing about subjective improvement in women before and after menopause.

Interestingly, recent studies have shown that methyl testosterone given orally is just as effective in the doses used as testosterone propionate injected intramuscularly. The dose required, however, is large; i. e. a minimum of 200 mg. per day, or a dose supplying a total of 30 Gm. within 5 months. The optimum dose of testosterone propionate appears to be 50 mg. intramuscularly three times per week—a dose which supplies a total of 3.0 Gm. in 3 or 4 months' time. Larger doses have not proved more effective.

There are always undesirable effects to be expected with testosterone therapy, and the patient must be warned of these and allowed to accept or reject the treatment as she wishes. Undesirable effects which have been observed include those in the dose range advised in table 5.

Increased libido may be so intense as to be decidedly bothersome. However this symptom is noted with less frequency on extremely high doses of testosterone than with smaller ones. In patients receiving 75 mg. per week, the symptom is present in 36 per cent. It appears in 27 per cent of those receiving 150 mg. per week, and in only 19 per cent receiving 600 mg. per week.

Testosterone is used principally for inoperable mammary cancer in premenopausal women and in women with bone lesions at any age. The optimum dose is 150 mg. per week. Before abandoning the possibility of response, a minimum dose of 3 Gm. in 3 months should be prescribed.

Irradiation of the breast or metastatic lesions prior to steroid therapy lessens the sensitivity of the lesion to the steroid effects. Although Garland[17] et al recently investigated this problem, their results are inconclusive on combined irradiation and steroid therapy as an asset or detriment to a comfortable life. It was their impression that such treatment should be used serially and not simultaneously.

Castration for Prostatic Cancer

The intimate relationship of androgens to prostatic cancer was illustrated by Moore[18] who examined the prostates of 252 men who died between the ages 41 and 90 and found 20 per cent malignant. The same author, after careful search, was unable to find any record of prostatic carcinoma in a patient who had eunuchoidism or any evidence of benign hypertrophy among 28 careful autopsies on men who had eunuchoidism, eunuchism, or pituitary infantilism arising before the age of 40.

Since 1935, interest has steadily increased regarding the relationship between hormones and prostatic cancer. At that time Kutscher and Wolbergs[19] isolated prostatic phosphatase and showed that it was active in acid solution. In 1936, Gutman and Sproul[20] discovered that acid phosphatase existed in metastases from prostatic carcinoma, and it was demonstrated that this substance did not exist in the infant prostate although present normally in the adult.

Since that time, the estimation of acid phosphatase in the blood has become

Table 3

SIDE EFFECTS OF STILBESTROL IN PER CENT

	Per Cent
Pigmentation areolae	46
Nausea	33
Edema	33
Bleeding	26
Vomiting	19
Incontinence	10
Hypercalcemia	3

Table 4

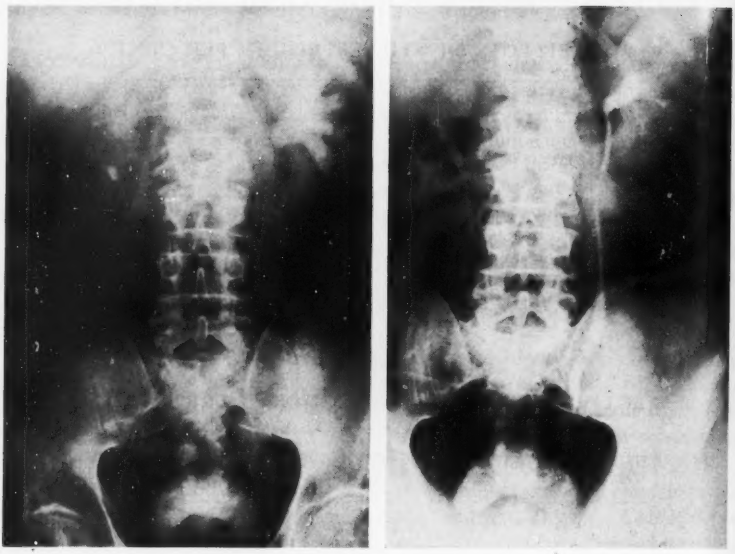
SUBJECTIVE RESPONSE TO STEROIDS IN BREAST CANCER
(740 Cases)

	Per Cent Relieved	
	Premen.	Postmen.
Testosterone propionate	51%	58%
Methyl testosterone		53%
Diethylstilbestrol	11%	39%
Ethinyl estradiol		59%

Table 5

SIDE EFFECTS OF TESTOSTERONE

With a dose of 150 mg. per week	
	Per Cent
Voice change	69
Hirsutism	65
Edema	29
Acne	29
Increased libido	27
Flushing	22
Nausea	12
Hypercalcemia	8
Vomiting	6



(a) (b)

Fig. 2. (a) Shows left hydronephrosis due to obstruction at ureterovesicle junction. Metastatic glands. (b) Marked improvement in left hydronephrosis after 4.0 mg. of stilbestrol daily for 30 days.

a diagnostic procedure of considerable value in the spread of carcinoma of the prostate. Dean[21] states that there is an increase in acid phosphatase in 73 per cent of patients in whom prostatic cancer has grown through the gland capsule. Metastases may be present, however, in some cases in which the acid phosphatase level is normal. Alkaline phosphatase, conversely, is high in nearly all cases of metastases of prostatic cancer to the bone, indicating the activity of bone defense. It may be high also in liver disease.

The experimental work of Huggins[11] has served as a great impetus in this field. Especially impressive was his demonstration that, in dogs in which the prostate was isolated from the bladder, androgen treatment caused a metaplasia of the prostate cells simulating cancer while estrogen treatment restored the gland to normal.

Following this, orchiectomy became a popular treatment for cancer of the prostate in patients in whom complete excision of the growth did not seem feasible.

Although many reports are available, only three will be mentioned. Dean[21] recorded the results of 31 cases treated by castration and followed for 6 months. The immediate effects were startling. Almost without exception, pain disappeared within 48 hours; appetite improved, weight increased, strength returned and soft tissue and lung metastases disappeared. The prostatic size

diminished little. Some improvement in skeletal metatases was seen. The acid phosphatase levels were elevated in 19 of 26 patients in whom this estimation was made while in 16 it fell promptly. Alkaline phosphatase tended to rise. After an average period of improvement lasting about 8 months relapses occurred.

Huggins[11] reported 5 year results of the treatment of prostatic cancer by orchiectomy in 20 cases in which 4 had no clinical or laboratory evidence of cancer and 1 had slowly advancing disease. All these patients had had widespread metastases and elevated serum phosphatase levels at the time of orchiectomy. After 5 years the phosphatase levels were normal and the skeletal metastases had disappeared or were equivocal.

Vest[15] has compared the survival rate in two groups of 74 patients, one group having undergone castration. Data from a 6 year follow-up study indicates that the total fatalities in the noncastration group totaled 82 per cent as contrasted with 43 per cent in the castration group.

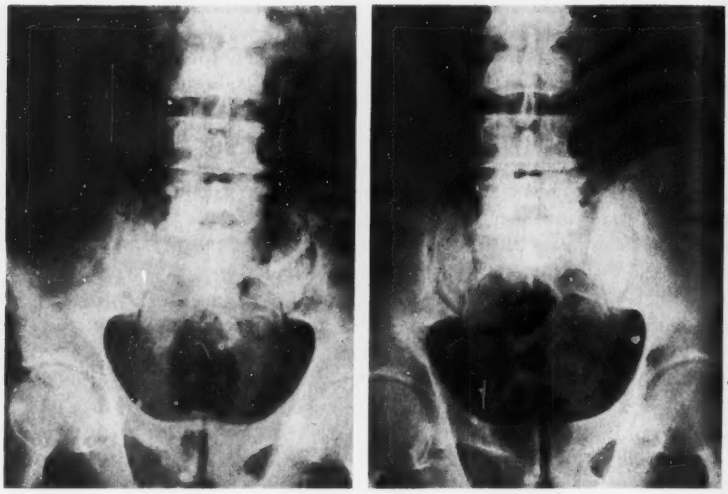
Studies of hormone excretion are interesting in relation to castration. Gonadotrophins rise to high levels, estrogens tend to fall and, most significant, 17-ketosteroids after an initial fall tend to rise above pretreatment levels.[22,23] This suggests that the adrenal androgens increase, a condition which may be connected with the occurrence of a common exacerbation. However, no rise in 17-ketosteroids follows the use of estrogens under similar circumstances.

Estrogens in Prostatic Cancer

Stilbestrol, or other estrogen therapy in inoperable prostatic cancer, has largely supplanted castration. The dosage varies widely. In our experience 2.0 mg. per day was insufficient to lower urinary gonadotrophins to below normal, although 6 mg. per day did so satisfactorily. Theoretically, it is highly desirable to lower pituitary gonadotrophin production in order to remove stimulus to androgen production. Whether or not doses of 30 mg. per day are more satisfactory than 10 mg. has not been clearly demonstrated.

Undesirable effects include impotence, severe irreversible damage to the testes (fig. 2a and b) and gynecomastia. It would seem highly inadvisable to withdraw estrogens after testicular damage has been brought about because pituitary hyperactivity would ensue and probably increase the output of adrenal androgens. It is advisable, therefore, once having started stilbestrol to continue it. Occasionally, nausea or vomiting, muscle pains or edema interfere with therapy. The accompanying mammary hypertrophy[24,25,26,27] may give rise to carcinoma which, when it occurs, is usually bilateral.

Results are slower than those following castration. Symptoms are often well-controlled when due to metastases and, although the size of the prostate may not alter significantly, lymphatic glands may be reduced in such a way as to relieve ureteral obstruction (fig. 3a and b). The common osteolytic lesions of the hip and spine apparently become denser and the bone outlines more normal in appearance. Dense osteoblastic lesions may disappear as may large osteolytic lesions in the skull, even on such small doses as 2.0 mg. per day.



(a) (b)

FIG. 3. (a) Extensive skeletal metastases from carcinoma of prostate. (b) Striking diminution in evidence of metastases after 21 months of stilbestrol therapy (total dosage 1649 mg.)

Such small doses, however, are considered undesirable.

An interesting comparison of estrogens and orchiectomy in prostatic cancer has been made by Nesbit.[28] In a large number of his patients demonstrating no metastases when first seen, orchiectomy plus stilbestrol therapy was definitely more valuable than either alone. The combined procedure was followed by a survival rate of 66 per cent in 3 weeks, whereas either method used alone resulted in a survival rate of only half the patients treated. In untreated patients, only 22 per cent lived for 3 years.

In patients in whom metastases were evident on first observation, stilbestrol did not produce results as satisfactory as those following orchiectomy alone or orchiectomy plus estrogen therapy. When metastases were present, combined orchiectomy and estrogen therapy were little better than orchiectomy alone.

During treatment it is interesting to follow the serum calcium, phosphorus and phosphatase levels. Acid phosphatase is elevated in about 75 per cent of cases, especially when the cancer has escaped beyond the prostatic capsule. In the course of improved cases the levels often fall to normal and, in the event of improvement of skeletal lesions, there may be a several-fold increase in the levels of alkaline phosphatase. Relapse occurs in most instances after 7 or 8 months of treatment. In older men the condition, even though cured, is kept in such complete control that the patient outlives his cancer to succumb to some other disorder.

References

1. Beatson, G. T.: On treatment of inoperable cases of carcinoma of mamma; suggestions for new method of treatment with illustrative cases. Lancet **2**:104 and 162, 1896.
2. Adair, F. E., Treves, N., Farrow, J. H. and Scharnagel, I. M.: Clinical effects of surgical and x-ray castration in mammary cancer. J.A.M.A. **128**:161 (May 19) 1945.
3. Farrow, J. H.: Effect of sex hormones on skeletal metastases from breast cancer. Endocrinology of Neoplastic Diseases. A symposium. Twombly, G. H. and Pack, G. T., editors. New York, Oxford University Press, 1947, p. 187-188.
4. Leucutia, T.: Value of orchiectomy in treatment of carcinoma of male breast. Radiology **46**:441 (May) 1946.
5. Treves, N., Abels, J. C., Woodard, H. Q. and Farrow, J. H.: Effects of orchiectomy on primary and metastatic carcinoma of breast. Surg., Gynec. and Obst. **79**:589 (Dec.) 1944.
6. Farrow, J. H. and Adair, F. E.: Effect of orchidectomy on skeletal metastases from cancer of male breast. Science **95**:654 (June 26) 1942.
7. Nathanson, I. T.: Hormonal alteration of advanced cancer of breast. S. Clin. North America **27**:1144 (Oct.) 1947.
8. Haddow, A., Watkinson, J. M. and Paterson, E.: Influences of synthetic oestrogens upon advanced malignant disease. Brit. M. J. **2**:393 (Sept. 23) 1944.
9. Discussion on advanced cases of carcinoma of breast treated by stilbestrol. Proc. Roy. Soc. Med. **37**:731, 1944.
10. Circular Letter No. 36. Subcommittee on Steroids and Cancer. Committee on Research of the Council on Pharmacy and Chemistry of the American Medical Association. Oct. 27, 1950.
11. Huggins, C.: Prostatic cancer treated by orchiectomy; 5 year results. J.A.M.A. **131**:576 (June 15) 1946.
12. Nathanson, I. T.: Endocrine aspects of human cancer. Recent Progress in Hormone Research, vol. 1. Pincus, G., editor. New York, Academic Press, 1947, p. 261-291.
13. Nathanson, I. T.: Effect of stilbestrol on advanced cancer of breast. Cancer Research **6**:484 (Sept.) 1946.
14. Huggins, C. and Hodges, C. V.: Studies on prostatic cancer; effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of prostate. Cancer Research **1**:293 (April) 1941.
15. Vest, S. A. and Frazier, T. H.: Survival following castration for prostatic cancer. J. Urol. **56**:97 (July) 1946.
16. Fergusson, J. D.: Carcinoma of prostate treated with oestrogens. (Hunterian lecture, abridged). Lancet **2**:551 (Oct. 19) 1946.
17. Garland, L. H., Baker, M., Picard, W. H. and Sisson, M. A.: The comparative effectiveness of roentgen and steroid hormone therapy in mammary cancer metastatic to bone. Read by invitation before the sixth International Congress of Radiology. London. July 23-29, 1950.
18. Moore, R. A.: Symposium on endocrinology of neoplastic diseases; benign hypertrophy and carcinoma of prostate; occurrence and experimental production in animals. Surgery **16**:152 (July) 1944.
19. Kutscher, W. and Wolbergs, H.: Prostataphosphatase. Ztschr. f. physiol. Chem. **236**:237, 1935.
20. Gutman, E. B., Sproul, E. E. and Gutman, A. B.: Significance of increased phosphatase activity of bone at site of osteoplastic metastases secondary to carcinoma of prostate gland. Am. J. Cancer **28**:485 (Nov.) 1936.
21. Dean, A. L., Woodard, H. Q. and Twombly, G. H.: Endocrine treatment of cancers of prostate gland. Surgery **16**:169 (Aug.) 1944.

22. Scott, W. W. and Vermeulen, C.: Studies on prostatic cancer; excretion of 17-ketosteroids, estrogens, and gonadotropins before and after castration. J. Clin. Endocrinol. **2**:450 (July) 1942.

23. Satterthwaite, R. W., Hill, J. H. and Packard, E. F.: Experimental and clinical evidence on role of 17-ketosteroids in prostatic carcinoma. J. Urol. **46**:1149 (Dec.) 1941.

24. Darget, R.: Epithelioma bilateral de la glande mammaire a la suite se L'emploi prolonge d'un oestrogene de synthese dans le traitment d'un cancer prostatique. Bull. et mem. A. franc. d'urol. 1946.

25. Abramson, W. and Warshawsky, H.: Cancer of breast in male, secondary to estrogenic administration; report of case: J. Urol. **59**:76 (Jan.) 1948.

26. Reimann-Hunziker, G.: Brustdrusenkarzinom nach Ovocyclinbehandlung eines Prostatakarzinoms. Helvet. chir. acta. **15**:242 (July) 1948.

27. Huggins, C.: Endocrine substances in treatment of cancers. J.A.M.A. **141**:750 (Nov. 12) 1949.

28. Nesbit, R. M. and Baum, W. C.: Prostatic carcinoma. J.A.M.A. **143**:1317 (Aug. 12) 1950.

LARGE GASTRIC BEZOAR

Report of a Case Treated Medically

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GASTRIC bezoars are rare medical curiosities. They are considered of historical interest because animal bezoars were thought, in the Middle Ages, to possess certain curative powers. Among the crown jewels of Queen Elizabeth were two large bezoar stones. The bezoar was listed in the London pharmacopeias until the mid-eighteenth century. DeBakey and Ochsner[1] state, "It neutralized poisons, reanimated old age, destroyed venoms, and counteracted attacks of vertigo, epilepsy, dysentery, plague, leprosy, etc."

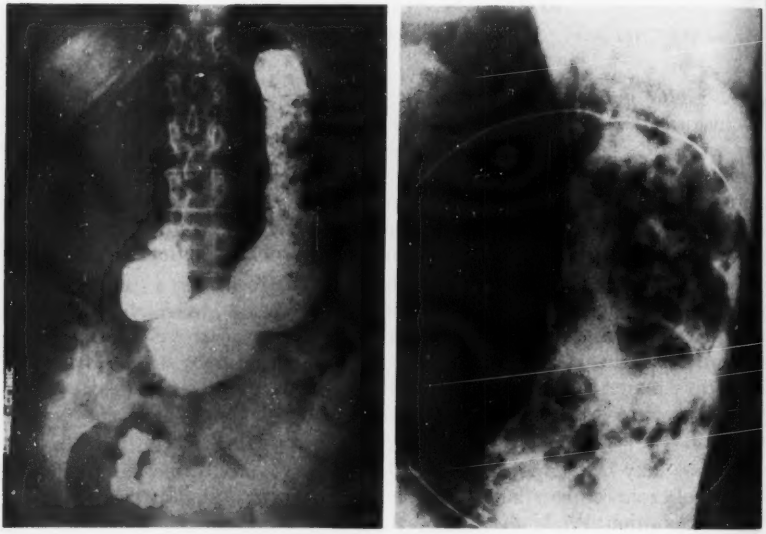
Bezoars are unusual in humans. DeBakey and Ochsner[1] in a careful review of the literature were able to find only 303 collected cases, to which they added 8 of their own in 1938. These foreign bodies occur most frequently in the psychiatric patient who has formed the habit of eating hair, string, and other indigestible materials. The incidence of bezoars outside psychiatric institutions is extremely rare, and the case we are reporting is the only one ever observed at the Cleveland Clinic.

Bezoars may be composed of several different materials, the most common the trichobezoar or hair ball. Next in incidence is the phytobezoar, of vegetable composition. While the most ordinary type originates from persimmon seeds,[2] it may be caused by other types of vegetable and plant substance. The third type of bezoar is the concretion, which may result from the ingestion of furniture polish for its alcoholic content—the shellac being precipitated and forming a gummy bezoar. Other concretions have been caused by bismuth, magnesium, calcium and sodium carbonates, and by salol.[3]

The symptoms and clinical manifestations in 131 collected cases of trichobezoar and 94 cases of phytobezoar were analyzed by DeBakey and Oshsner[1] whose observations are presented:

Manifestation	Trichobezoar (Per cent)	Phytobezoar (Per cent)
Abdominal mass	87.7	57.4
Pain and tenderness	70.2	85.1
Nausea and vomiting	64.9	74.4
Weakness and loss of weight	38.1	32.9
Constipation and diarrhea	32.0	31.9
Hematemesis	6.1	14.8

As may readily be seen from the table, the symptoms are similar to those often observed in advanced carcinoma of the stomach. If there is no history of ingestion, the diagnosis may be confused with carcinoma. By their irritative action bezoars may cause a superficial gastritis, or even a fairly large gastric ulcer, which may further complicate the problem of diagnosis and treatment. The diagnosis is usually made by roentgen examination, the bezoar having formed a movable mass within the stomach. Patterson and Rouse[4] have reported 5 cases observed on gastroscopic examination, which may assist in diagnoses.



(a) (b)

FIG. 1. (a) Roentgenogram of stomach showing filling defect extending from angulus to cardia. Gastroscopically, this was one large mass instead of multiple defects as suggested by x-ray. (b) Spot film showing same filling defect.

With few exceptions the treatment of bezoars has necessarily been surgical. No successful method of dissolving the sticky gums and hair which make up their bulk has been reported, although Mills and Simpson (quoted by Hart[2]), succeeded in removing one bezoar by means of hydrochloric acid and Weitzen[5] was able to remove a trichophytobezoar by gastric lavage. If attempted medical treatment is not immediately effective, early surgical intervention is indicated; this should not be delayed until the patient develops a gastric ulcer and hematemesis, as these complications increase the risk of operation.

The following report of a bezoar caused by vegetable starch is the only case on file at the Cleveland Clinic, and an instance in which successful removal was accomplished without recourse to surgery.

Case Report

A 56-year-old Negress was admitted to the hospital for diabetic management. She had enjoyed reasonably good health and her past history was entirely negative. Positive physical findings included blood pressure of 180/110, moderate arteriosclerosis, hemorrhagic retinopathy, and lenticular opacities. No abdominal mass was palpable. Blood count was normal, and Wassermann and Kahn blood tests were negative. Urine was 4 plus for sugar, and fasting blood sugar was 222 mg. per cent.

While in the hospital the patient complained of some loss of appetite and nausea, although there was no previous history of gastrointestinal disturbance. A roentgen examination of the stomach showed multiple filling defects which were considered due to the presence of food. The stomach was aspirated the next night, and the roentgen examination was repeated. The appearance was the same as on the initial examination, with multiple filling defects apparent. A polypoid type of infiltrative lesion, a bezoar, and retained food were all suggested by the roentgenologist as possible diagnoses (fig. 1a and b). Continuous suction was instituted the following night and the x-ray examination, when repeated, showed the identical lesion previously observed. Because of the persistence of the multiple filling defects, despite aspiration of the stomach, the roentgenologist made the diagnosis of an infiltrative lesion involving the mucosa of the stomach.

The next day gastroscopy was performed. The mucosa of the antrum was normal. Approximately two-thirds of the stomach, extending from the angulus to the cardia, was filled with a large bezoar. It appeared rather hard and concrete, was covered largely with barium, and measured about 9 to 10 cm. in length and 3 to 5 cm. in diameter.

On further interrogation, the patient denied the ingestion of furniture polish, shellac, or persimmon seeds, although she admitted having eaten laundry starch "for the menopause," a practice not uncommon among her race. Because the patient was diabetic and hypertensive, and because she exhibited neither symptoms nor evidence of complications, it was thought advisable to attempt to wash out the bezoar. It was our opinion, however, that surgery would be necessary.

The same night 4 ounces of a 1 per cent hydrogen peroxide solution and mineral oil were instilled, and the stomach was aspirated with a large Ewald tube every 10 minutes for 4 hours. The return (1600 cc.) consisted of frothy-appearing spinach and salmon, and considerable amorphous material. The patient was continued on a liquid diet; the stomach was washed and aspirated in a similar manner for the following 3 nights. White and yellow particles and amorphous material were obtained.

Gastroscopic examination was repeated in 4 days and, surprisingly, no evidence of the bezoar remained. The entire antrum and pylorus were normal. In the body of the stomach patchy atrophic changes were apparent, as well as small petechial hemorrhages, and one superficial erosion. Subsequent roentgen examination was normal (fig. 2).

Discussion

An unusual case of a phytobezoar caused by ingestion of laundry starch has been presented. Roentgen examination (fig. 1a and b) was most suggestive of an infiltrative, polypoid lesion. The diagnosis was established by gastroscopic examination which, in this instance, was of primary diagnostic importance.

Aspiration of the stomach and all night suction with a Levine tube failed to change the appearance of the bezoar on repeated x-ray examinations. Instal-

FIG. 2. Roentgenogram of stomach after bezoar had been removed. No signs of any filling defect.

lation of a 1 per cent hydrogen peroxide solution and mineral oil, and the subsequent aspiration of the stomach with the large Ewald tube for 4 hours daily on the succeeding 4 days, resulted in removal of the bezoar. The success of the procedure was established not only by the material obtained, but also by subsequent gastroscopic and roentgen examinations.

It is suggested that further short trials be made at aspiration of the uncomplicated phytobezoar, accompanied by instillation of 1 per cent hydrogen peroxide and mineral oil, before referring these patients to the surgeon.

References

1. DeBakey, M. and Ochsner, A.: Bezoars and concretions. Surgery **4**:934 (Dec.) 1938 and **5**:132 (Jan.) 1939.
2. Hart, W. E.: Phytobezoars. J.A.M.A. **81**:1870 (Dec. 1) 1923.
3. Bockus, H. L. and others. Gastroenterology, vol. 1. Philadelphia, W. B. Saunders Company, 1946, p. 762-769.
4. Patterson, C. O. and Rouse, M. O.: Foreign bodies in stomach observed through gastroscope; report of 5 cases. Texas State J. Med. **36**:238 (July) 1940.
5. Weitzen, M.: Chronic gastritis caused by gastric bezoar. New York State J. Med. **40**: (part 1) 136 (Jan. 15) 1940.

THE ROLE OF THE GEIGER COUNTER IN A MEDICAL INSTITUTION

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GEIGER counters have aroused more interest in the minds of both professional and lay people than any other topic pertaining to atomic energy. A Geiger counter is an exceedingly sensitive apparatus for detecting and evaluating ionizing radiations such as x-rays, alpha, beta, and gamma rays of radium or radioactive isotopes, protons, deuterons or neutrons.

Many believe the Geiger counter is of recent origin and a product of the atomic age. That is not so. The principle of the Geiger counter was discovered decades before the first chain reacting atomic pile was successfully launched at Stagg Field of the University of Chicago, on December 2, 1942. Hans Geiger, a German physicist working with Rutherford at the University of Manchester in England, developed the first "electrical method of counting alpha particles" in 1908.[1] In 1912 Geiger and Rutherford reported on an improved method which permitted the recording of 1000 alpha particles per minute. One year later Geiger constructed a counter for beta ray particles but it was not until 1928 that he, in collaboration with Walther Mueller, perfected the modern version of the tube for measuring all types of radiations. Therefore the Geiger counter is often now referred to as the Geiger-Mueller tube, although the principle of the new construction is the same as the original one.

Essentially the Geiger counter consists of a glass or metal tube filled with air or other combinations of gases at low pressure. Two insulated electrodes penetrate the wall of the tube and a critical electric potential difference is maintained between them. This potential is high, i. e. slightly below the point where ionization by shock or that which is commonly called "corona discharge" would take place.

At the annual meeting of the American Association for the Advancement of Science (Cleveland) in 1930, we presented a photoelectric Geiger counter with a recording string electrometer which we had built ourselves.[2] This apparatus was soon improved noticeably as far as sensitivity and selectivity were concerned.[3] Since it was designed primarily for the detection and possible measurement of Gurwitsch's "mitogenetic radiation"[4] it was made especially sensitive to ultraviolet rays in the region of 2200 angstroms. This investigation of the detection of mitogenic radiation with the Geiger counter tube was continued for several years, notably in collaboration with Hans Barth who had been a co-worker with Gurwitsch. Barth built about fifty Geiger counter tubes[5,6] which extended over wide ranges of sensitivity and responses to limited parts of the electromagnetic spectrum.

While none of these studies led to positive results regarding the existence of mitogenetic radiations, they did produce substantial improvements in our

Geiger counter tubes and recording devices which in turn led to new uses for these counters.

In 1935, while investigating some phenomena of artificial radioactivity with our ultraviolet-sensitive counter we observed that the ultraviolet phosphorescence of certain salts, notably of pure sodium chloride, persisted for unexpectedly lengthy periods following their exposure to and removal from roentgen rays of radium; for years, as we subsequently learned. We noticed especially, however, that this ultraviolet phosphorescence increased conspicuously when the irradiated compounds were exposed to visible light.[7,8] This discovery aroused instant repercussions along biologic and physical lines and the question was raised of a possible bactericidal effect of these short wave ultraviolet radiations.[9]

The physical literature contains descriptions of numerous investigations which followed the publication of our studies on the ultraviolet phosphoresence of irradiated salt; the last one refers to the fundamental importance of these observations for the detection of scintillations from crystals when bombarded by nuclear particles.[10]

Other major uses to which we put our improved Geiger counters were: making surveys for radiation protection at places where radium and notably radon were stored or used on patients; for surveys of possible contamination from leaking radium tubes or in the radon plant and, finally, for locating lost radium or radon tubes and seeds. We developed portable counter tubes and indicating units. These were completed in 1936 and the first two instances of locating lost radium tubes with a Geiger counter occurred on July 15, 1937 in Cleveland and, through a coincidence, on the following day in a Canton, Ohio hospital. In both cases the radium tubes were found within a few minutes after the search was instituted, in contrast to the many hours required previously when we utilized the old-type gold leaf or string electroscopes.[11] The fact that the Geiger counter permitted the location of lost radium tubes or needles within a few minutes after doctors and nurses had often conscientiously searched the treatment room for hours and sometimes days was, of course, startling to professional and lay people.

The Cleveland News commented on these activities on August 5, 1937: "The fame of O. G., physicist at the Cleveland Clinic, and his assistant, I. E. B. as hunters of lost particles of radium, apparently has spread far. Their latest search took them to a hospital in Akron where, with their Geiger counter, they found 50 mg., or $2,500 worth of radium in the ashes of an incinerator. The search took only 10 minutes with the sensitive instrument I. E. B. developed. The Akron hospital attaches had read in the *News* of the success of the Clevelander's search for $500 worth of radium at a hospital here, and summoned them as soon as the loss in Akron was reported."

These same counters were used to measure the first cyclotron-produced radioactive isotopes which we received in 1941 and 1943. With the advent of atomic fission and the abundance of pile-produced radioactive isotopes the demand for Geiger counters rapidly increased to fantastic proportions. Today there are more than 40 companies in this country producing Geiger counters

of many kinds. The growth of our own isotope department from its modest beginnings to the present status was described recently in detail.[12] We have in our department, besides the home-built instruments, Geiger counters which vary from compact portable designs for quick patient check-ups and protective monitoring to cumbersome but completely automatic devices which measure and record the radioactivity up to 25 samples of blood, urine or tissues from patients having had administrations of radioactive isotopes. Special directional counters are being used to study the uptake and distribution of radioactive iodine in patients with thyroid diseases. Similar counters are employed in localizing brain tumors after injection of diiodofluoresceine. Probe-like counters are used for measurement of radioactivity in body cavities or open wounds or to study the distribution of radiation around a series of radium needles or tubes which have been inserted into tumors for therapy purposes. Surveys of proper protection around x-ray tubes and any radioactive materials are quickly made with portable Geiger counters.

Opportunities are unlimited for further development of radiation-counting equipment to solve problems in medicine.

References

1. Rovner, L.: Geiger Counters, Counter Apparatus, Crystal and Scintillation Counters. In Medical Physics II (Glasser, O., editor). Chicago, Year Book Publishers, 1950, p. 345.
2. Glasser, O. and Seitz, V. B.: Physical detectors of mitogenetic radiation. Bull. Am. Phys. Soc. **5**:6, 1930.
3. Glasser, O.: The Detection of Mitogenetic Radiation. Atti del I Congresso Internazionale di Elettro-radio-biologia, Vol. II. Venice, Italy, 1934, p. 778.
4. Idem: Mitogenetic Radiation. In Medical Physics I (Glasser, O., editor). Chicago, Year Book Publishers, 1944, p. 760.
5. Glasser, O. and Barth, H.: Studies of problem of mitogenetic radiation. Radiology **30**:62, 1938.
6. Idem: Further studies on problem of mitogenetic radiation. Radiology **33**:25, 1939.
7. Glasser, O. and Beasley, I. E.: Induced ultraviolet fluorescence and its release by visible light. Phys. Rev. **47**:570, 1935.
8. Idem: Release of ultraviolet radiation from roentgenized substances by visible light. Am. J. Roentgenol. **36**:381, 1936.
9. Idem: Bemerkungen zu der Arbeit "Ueber die bakterizide Wirkung des mit Radium bestrahlten Kochsalzes auf Streptokokken und seine Radioaktivitaet." Tohoku J. Exp. Med. **32**:411, 1938.
10. Mandeville, C. E. and Albrecht, H. O.: Detection of scintillations from crystals with photo-sensitive Geiger-Mueller counter. Phys. Rev. **79**: 1010, 1950.
11. Taft, R. B.: Radium Lost and Found. Charleston, S. C., Furlong, 1938. Radium Lost and Found, ed. 2. Charleston, S. C., Walker, Evans and Cogswell, 1946.
12. Glasser, O.: Evolution of radiologic physics as applied to isotopes (Janeway Lecture). Am. J. Roentgenol. **65**:515, 1951.

PRIMARY LINITIS PLASTICA CARCINOMA OF THE COLON

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THE primary linitis plastica type of carcinoma of the colon is rare. Although David[1] reported an instance of this lesion in 1931, no mention of examination of the stomach was made at the time of surgical exploration. In 1936 Dixon and Stevens[2] reviewed 37 cases of linitis plastica carcinoma of the colon and presented an additional 6. In all but the case reported by David, the lesion was secondary to gastric neoplasm of the linitis plastica type. More recently, Laufman and Saphir[3] have added 4 instances of unequivocal primary carcinoma of the colon of this variety. Necropsy failed to reveal any evidence of gastric carcinoma or other attributable primary sites. All their cases were diagnosed clinically as ulcerative colitis prior to surgery or necropsy; in 2 this disease was an additional finding. A similar lesion has been encountered recently at the Cleveland Clinic Hospital. Clinically and roentgenologically its resemblance to ulcerative colitis resulted in a tenable preoperative diagnosis of this disease. Its true nature was revealed at the time of operation only after the bowel was opened for pathologic examination. Careful exploration of the stomach failed to reveal any abnormality. It appears probable that our case is another instance of primary linitis plastica carcinoma of the colon.

Case Report

A professional baseball player, aged 34, was seen for the first time at the Cleveland Clinic on December 29, 1950, complaining of intermittent diarrhea and symptoms indicating intestinal obstruction. One of us (B. D. R.) had observed this patient at the inception of his disease 20 years previously (1931) when he was admitted to a hospital complaining of bloody diarrhea, malaise, weight loss, abdominal pain and fatigue. The diagnosis at that time was chronic nonspecific ulcerative colitis. Stool cultures were negative for pathogens and no amebae were found. Proctosigmoidoscopic examination was compatible with the above diagnosis. X-rays of the colon were interpreted as follows: "There is no definite evidence of an organic lesion of this colon. The entire bowel is quite irritable and somewhat tender to palpation. The appendix is not visualized."

Except for occasional loose stools the patient was well until 1943 at which time his symptoms returned and he was again hospitalized. Unfortunately, x-rays taken at that

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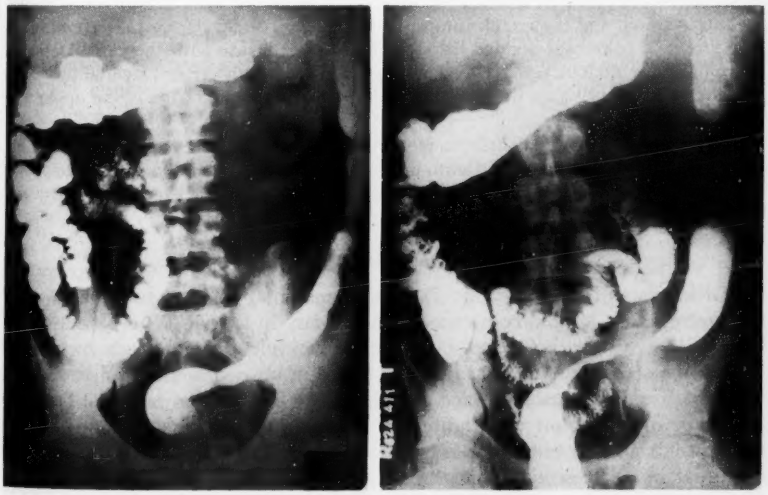
time are not available for study, but the report from the record was as follows: "A barium enema filled the entire colon and entered the terminal ileum. The colon was spastic in character and showed repeated heavy spasms during filling. There was an absence of haustral markings throughout. A few areas along the descending colon are suggestive of rather large ulcerations. **Impression:** Ulcerative colitis."

In July 1947, the patient again consulted one of us (B. D. R.) because of recurrence of symptoms. He stated that he had been in good health since 1943 and able to play professional baseball until recently. Proctosigmoidoscopy showed the rectal mucosa to be granular and friable. Roentgen films of the colon (fig. 1a) at that time showed early changes suggesting chronic ulcerative colitis, particularly in the sigmoid colon. During 1947 and 1948, he was seen on frequent occasions and treated with sulfasuxidine. Periodic sigmoidoscopic examinations showed typical ulcerative colitis involving the rectum. The patient was not observed again until October 1950 when he experienced a particularly severe exacerbation consisting of eight to ten loose water stools daily, malaise, occasional bright red blood, and weight loss. He stated that deterioration appeared more rapid with this exacerbation than with previous ones.

Physical Examination: The patient was 69 inches in height. Although his usual weight was 240 pounds, at the time of examination his weight was 216. He claimed that he had lost 24 pounds in the previous 6 months. His temperature was 98.6 F., pulse 84 per minute and regular, blood pressure 135/85. His general appearance was satisfactory, although he was somewhat pale. General physical examination was normal. The abdominal musculature was so heavy that satisfactory examination was not possible;



(a) (b)

FIG. 1. Ulcerative colitis showing (a) generalized narrowing of the descending and sigmoid portions of the colon with loss of normal haustral markings; (b) colon 3 years and 3 months later with loss of haustrations in transverse and descending portions. Descending portion smooth. Long, narrowed segment involving sigmoid portions represents carcinoma.

however no masses were palpable. A tentative diagnosis of chronic, nonspecific ulcerative colitis was made.

Proctoscopic examination revealed the ampulla of the rectum to be almost obliterated by a stricture at 5 inches; there was evidence of diffuse inflammatory change at this point with profuse bleeding on swabbing. Roentgenograms of the colon (fig. 1b) were reported as follows: "The rectum appears to be of normal caliber. The entire sigmoid portion shows noticeable smooth narrowing for a distance of approximately 16 cm. It appears to be contracted. Descending portion is unusually smooth and there is an absence of normal haustral markings in the transverse portion. Stricture of sigmoid is most likely on the basis of ulcerative colitis rather than neoplasm. Changes in transverse and descending portions are suggestive of ulcerative colitis."

Because the patient continued to decline and because of the rather extreme stricture with obstruction present in the sigmoid colon, surgical intervention was indicated. Accordingly, on January 25, 1951, the left colon was approached through a low midline incision, which was extended past the umbilicus to the left costal margin. The sigmoid colon with its mesentery and pericolic fat formed a large mass which nearly filled the pelvis. The descending colon was fixed and leathery and exhibited the hypertrophic changes attendant with chronic low grade obstruction. Transverse colon and cecum appeared normal as was the small bowel. Palpation of the stomach, duodenum and liver revealed no unusual findings. These observations suggested ulcerative colitis with a severe pericolitis of the sigmoid colon. Because of the localization of the disease, it was decided that the entire left colon should be removed and a splenic flexure colostomy performed in the left upper quadrant. The sigmoid colon was freed from the rectosigmoid upward, the left colon was mobilized in the usual manner, and the splenic flexure was liberated and drawn down to the midline. The colon was divided below through the rectosigmoid and the rectal stump was turned in. The pelvis was re-peritonealized. The proximal colon was divided through the splenic flexure with the Cope-DeMartel clamp, and the abdomen was closed through all layers with vertical steel alloy "figure of eight" sutures, bringing the colostomy out through the midportion of the upper limb of the wound.

The patient had an afebrile, uncomplicated, postoperative course and was discharged from the hospital on the tenth postoperative day. He has since gained 20 pounds and manages his colostomy efficiently enough to permit full time work.

Pathology

Gross Examination: (Fig. 2) The specimen consisted of a segment of descending and sigmoid colon measuring 30 cm. in length. Fifteen centimeters from the proximal line of resection and extending distally for a distance of 14 cm. the serosal surface was dull, gray and indurated as contrasted with the smooth glistening serosal surface of uninvolved bowel. The pericolic fat tissue in the involved region was indurated and greatly thickened. Upon opening the bowel a normal mucosal pattern was apparent in the first 15 cm. from the proximal line of resection and the lumen measured 5 cm. in cross diameter. The mucosal surface of the involved segment was finely granular, firm and gray, without evidence of distinct ulceration. The lumen measured only 1 cm. in cross diameter throughout this region. The wall was thick, gray and firm, converting the involved segment into a rigid tube. On cross section, finger-like projections of dense gray-white tissue extended into the pericolic fat for a dis-

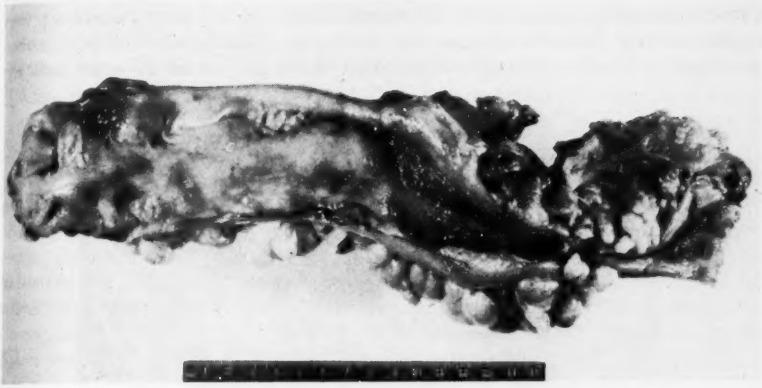


FIG. 2. Gross specimen. Note narrowed segment of bowel due to carcinoma.

tance of 3.5 cm. The mesentery was indurated and greatly thickened throughout. Twenty-nine lymph nodes were recovered from the pericolic adipose tissue and mesentery after alcohol-formalin fixation.

Microscopic Examination: (Fig. 3a and b) Sections of neoplasm revealed absence of normal mucosal glands. A thin layer of fibrinopurulent exudate lined the lumen and extended about the entire circumference of the bowel. Immediately beneath this layer was a malignant epithelial new growth characterized by large and small masses of atypical epithelial cells, for the most part polygonal in shape with round, vesicular nuclei. Atypical mitotic figures and hyperchromatic large nucleoli were numerous. In areas, small lumina were formed by these neoplastic cells. Large and small irregular cystic spaces were lined by these cells and contained blue-staining material. Individual cells lay free in these pools of blue-stained material. An occasional signet-ring cell was observed either alone or in small groups within the tumor stroma which was moderately dense. The signet-ring cell, however, was not an outstanding feature of the lesion. The tumor extended about the circumference of the bowel and invaded all muscle layers, serosa, and pericolic adipose tissue. A mild inflammatory infiltration of polymorphonuclear leukocytes and lymphocytes was noted throughout the lesion. Masses of tumor cells were present in small subserosal venules.

Twenty-eight of the twenty-nine lymph nodes demonstrated secondary carcinoma.

Sections of grossly uninvolved portions of bowel revealed a normal structure without increase in density of submucosa or atypical mucosal pattern.

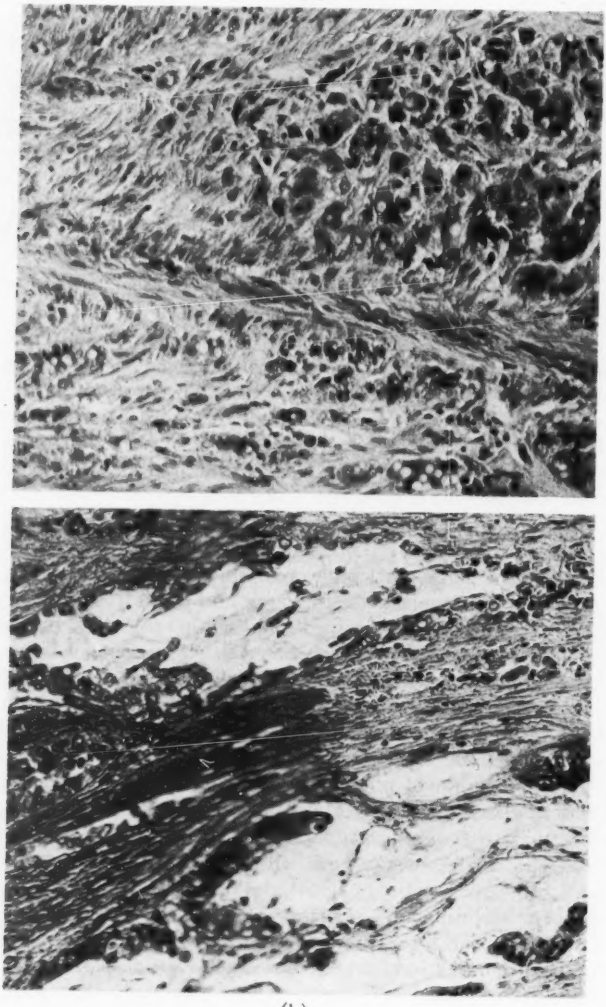
Diagnosis: Adenocarcinoma of colon; extensive linear and stenosing type—linitis plastica.

Discussion

The clinical and pathologic features of this case simulate those of primary linitis plastica carcinoma of the colon reported by Laufman and Saphir.[3] Al-

though ulcerative colitis was an additional finding in 2 of their cases, they were of the opinion that this disease was incidental. The detailed clinical, roentgenologic, and sigmoidoscopic observation of our patient for 20 years indicates

(a)



(b)

FIG. 3. (a) Photomicrograph showing spheroidal, dark-staining tumor cells in muscularis. Rare signet-ring type present (H & E x70); (b) mucinous pools formed by tumor (H & E x70).

that the initial disease of the intestinal tract was chronic ulcerative colitis. The presence of carcinoma in that segment of previously diseased bowel suggests neoplastic transformation of chronic ulcerative colitis rather than the possibility of coincidence. The involvement of such a long segment of bowel also favors the multicentric origin of this type as stressed by Willis[4] in his discussion of linitis plastica carcinoma of the stomach.

The diagnostic difficulties encountered in this type of neoplasm present a problem. Clinical, roentgenologic and sigmoidoscopic studies are apparently of little value in the detection of such a lesion arising in pre-existing ulcerative colitis. Patients with similar findings have been followed for years without any indication of neoplastic transformation. Does this imply that they should be subjected to resection of the colon even though their disease appears stationary except for occasional minor exacerbations? Although the rarity of this type of lesion would appear to make this procedure impractical for the group, the fact must be recognized that ulcerative colitis may undergo malignant transformation. Surgical therapy merits particular consideration in those cases in which areas of stricture occur as well as unusual change in a patient's symptomatology.

Primary linitis plastica type of carcinoma of the colon is of additional importance to the surgeon because the presence of such a lesion obviously necessitates more radical surgery than would be undertaken for chronic ulcerative colitis or other benign stenosing lesions of the colon. The validity of the term linitis plastica has provoked criticism and debate. Its entrenched position in medical teaching and literature makes its use imperative in the classification of this lesion. Histologically the tumor herein reported exhibits features attributed to linitis plastica carcinoma as outlined by Laufman and Saphir:[3] (1) spheroidal cells, (2) small, miniature new gland formations, and (3) mucin secreting cells. It should be emphasized, however, that many areas of the tumor were similar in histologic appearance to neoplasms frequently encountered in the large intestine not producing diffuse linear involvement.

Willis,[4] has used the term linitis plastica carcinoma to denote a special macroscopic type of neoplasm. He asserts that histologic variants do not denote entities but merely variants of one entity, while several or all histologic variants may be present in one tumor. Ewing[5] also stresses the inconsistency of histologic features in those neoplasms which convert the intestine into a rigid tube. It seems more logical to use the term linitis plastica as a gross descriptive one rather than as a connotation for certain microscopic features. The involvement of pericolic adipose tissue, as well as the extensive metastases to lymph nodes, indicates an extremely poor prognosis in this instance.[6]

Summary

1. A case of primary linitis plastica type of carcinoma of the colon arising in a previously existing chronic ulcerative colitis is reported.
2. Preoperative diagnostic difficulties are described.
3. A brief review and discussion of the literature is presented.

References

1. David, V. C.: Malignancy in linitis plastica. S. Clin. North America **11**:47 (Feb.) 1931.
2. Dixon, C. F. and Stevens, G. A.: Carcinoma of linitis plastica type involving intestine. Ann. Surg. **103**:263 (Feb.) 1936.
3. Laufman, H. and Saphir, O.: Primary linitis plastica type carcinoma of colon. Arch. Surg. **62**:79 (Jan.) 1951.
4. Willis, R. A.: Pathology of Tumors. St. Louis, C. V. Mosby Company, 1948, p. 402.
5. Ewing, J.: Neoplastic Diseases; a Treatise on Tumors, ed. 2. Philadelphia, W. B. Saunders Company, 1922, p. 640.
6. Dunning, E. J., Jones, T. E. and Hazard, J. B.: Carcinoma of rectum. Ann. Surg. **133**:166 (Feb.) 1951.

PHYSICAL THERAPEUTIC MEASURES IN HEMIPLEGIA

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THE management of a patient with hemiplegia is a difficult problem since many of the basic factors are not understood. In general, the purpose of such a program is the prevention and correction of deformities, increase of muscle function, and the instruction of the patient in performing the activities essential to daily living. It has been demonstrated by Dinken[1] that there are 22 basic activities regarding locomotion and traveling, 8 having to do with dressing, 7 in toilet activities, 8 concerned with eating, and 15 associated with hand function.

There is no set rule as to when the necessary physical measures should be initiated. It is important in cardiovascular accidents to attempt the differentiation of etiology, as there is a definite relationship in respect to early treatment.

Gilbert and deTakats[2] have listed the following differential points:

	Cerebral Embolism	Cerebral Thrombosis	Cerebral Hemorrhage
1. Onset	Sudden	Gradual (55%)	Sudden
2. Spinal fluid	Clear Normal pressure	Clear Normal pressure	Bloody Often slight increase in pressure
3. Average age	53	60.8	58.9
4. Average blood pressure	143/85	166/97	213/120
5. Predisposing disease	Rheumatic heart disease Bacterial endocarditis Postcoronary disease Hypertensive cardiovascular disease	Arteriosclerosis	Hypertension Congenital aneurysms

As a general rule, in those patients having a diagnosis of thrombosis or embolism, the indicated physical measures may be started immediately. In patients with a diagnosis of hemorrhage, little if any treatment should be started until the spinal fluid is clear or at least until the signs of meningeal irritation have practically subsided. Obviously, in some cases in which deformity seems to be developing, cautious passive exercises are indicated.

Usually the prognosis for functional recovery is best in patients who have had thrombosis and poorest in patients having experienced hemorrhage and emboli. Prolonged flaccidity is a poor prognostic sign and any muscle that

remains completely paralyzed after a period of 3 months is not likely to return to the point of satisfactory functional value. However, there are exceptions in these cases also. The greatest over-all return of function undoubtedly takes place in the 6 months subsequent to onset; thereafter it is only a matter of trying to improve the remaining function. Lengthy programs of treatment are not indicated even though relatives insist on continued therapy.

The initial step for any patient is a specific program of passive exercises, and only in patients critically afflicted should this be deferred. Each part of the involved extremity should be subjected to a full range of motion several times, and at intervals of two to three times daily. Special attention should be given to the shoulder, and it is most important that such exercises be taken with the shoulder girdle immobilized as well as freely movable. If there is any indication of periarthritis of the shoulder or shoulder-hand syndrome, stellate blocks should be given once daily, prior to the indicated exercises, except in instances where such a procedure is contraindicated because of hemorrhage. Pulley exercises are of great value when the patient is able to cooperate. In such cases relaxation becomes more spontaneous as the patient controls the stretching and, with the fear of being hurt thus minimized, will do a better job than with assistance. Such exercises also give an opportunity for reciprocal motion which is important in later functional activities.

When active motion starts to return, a program of careful assistive active exercises is instituted with the therapist guiding the extremity through a full range of motion. This is of utmost importance in gaining coordination, and in the early treatment to prevent substitution and bizarre motions. During this phase the therapist is essential in the development of satisfactory patterns; these may assure later independence in the efficient use of a weak muscle rather than encouraging reliance on strength alone. Free active exercises should be employed when a patient is able to move the part through a full range of motion in the horizontal plane. Resistive exercises to strengthen muscles are usually initiated after coordination has been established, and the member can be moved through a full range of motion against gravity.

Heat, massage, and electrical stimulation have little over-all value in the hemiplegic patient. Most persons enjoy heat and massage and most families request such measures. Heat does promote reflex relaxation as well as vasodilation to a moderate degree. Light stroking massage is relaxing and, when given correctly with the stroke in the direction of the venous and lymphatic return, will improve circulation to a mild degree. Heat and massage must not be employed at the expense of the exercises which are the most important part of the program. These measures may be carried out by the family, several times daily, with beneficial results.

When there is sufficient active motion of the upper extremity occupational therapy, stressing functional activities, should be started. Such therapy is an excellent means of improving coordination. Diversional activities, while useful, must be minimized in order that the patient may concentrate upon those procedures of greatest importance.[3]

Balance training should be begun as early as the condition of the patient permits. The patient should at first be supported by pillows in bed, then elevated to a sitting position. Next, the feet should be allowed to descend gradually over the side of the bed until, finally, a standing position is attained.[4]

Ambulation is essentially of great concern to both patient and family. When the motor power is severely restricted it is most important that one may speak and make one's wants known—a fact too often overlooked. The ability to use the hands and arms in order to insure independence regarding daily needs is more important than walking, since there are many ways and means of getting about if necessary.

Although no set rule can be established, the general procedure is initiated by standing at the side of the bed after the patient has experienced sufficient return of power in the hip flexors and knee extensors to be able to lift the leg 1 to 2 inches off the bed. Usually a patient who can stand will eventually walk. A heel-toe gait is taught in order to overcome the effects of any residual ankle clonus. Crutches and canes are of value and should be used in establishing balance and for assistance in stepping. Practice walking in parallel bars is advocated. Occasionally elevation of the normal foot by a plank, ¼ to 1 inch, is advised to allow clearance of the involved foot; this inhibits extensor spasm of the involved leg and may prove a worth-while supplementary aid. Later a lift on the shoe may be utilized.

Appliances have an important place in the over-all treatment program. Approximately 50 per cent of patients will need a leg brace. Most patients will require a short caliper with 90 degree ankle stop to control the drop foot and ankle clonus, plus an outside "T" strap placed well forward on the sole and cut back on an angle so as to control the inversion of the forefoot. This gives the patient a firm base upon which to stand and walk. A few patients with especially weak quadriceps will need long leg braces; these patients must be studied carefully as they often have concomitant involvements such as disturbance of balance, vision and hands, which prohibit the effective use of a brace.[5]

Splints are often needed for the fingers and wrist as flexor power usually returns first. Often the extensors are so over-stretched they never have the opportunity of regaining their normal resting length or functioning to any degree of efficiency when active return is limited.

Such a program obviously occupies a long period of time with the greater part of treatment conducted on an outpatient basis. As few patients experience complete return of function, varying degrees of disability are to be expected. Since this eventually becomes a family problem the cooperation and intelligent help of relatives is important. They should be introduced into the program early in the course of therapy, thereby insuring better adjustment to the ultimate problem.

Obviously, a daily program for the patient is essential and best regulated by the family with assistance and supervision of a trained therapist. Much later, depending upon the development of functional and ambulatory activities, consideration should be given to the question of vocational possibilities; these, for most hemiplegic patients, are greatly limited.

References

1. Dinken, H.: Evaluation of disability and treatment in hemiplegia. Arch. Phys. Med. **28**:263 (May) 1947.
2. Gilbert, N. C. and deTakats, G.: Emergency treatment of apoplexy. J.A.M.A. **136**:63 (March 6) 1948.
3. Dinken, H.: Physical treatment of hemiplegic patient in general practice. J.A.M.A. **139**:1255 (April 30) 1949.
4. Covalt, D. A., Yamshon, L. J. and Nowicki, V.: Physiologic aid to functional training of hemiplegic arm. Am. J. Occup. Therapy **3**:286 (Nov.-Dec.) 1949.
5. Covalt, D. A.: Rehabilitation of hemiplegic patient. Phys. Therapy Rev. **29**:514 (Nov. 1949.

CYSTOSARCOMA PHYLLODES MAMMAE, FIBROSARCOMA VARIANT

A Case Report

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THE term cystosarcoma phyllodes, originating more than a century ago is attributed to Johannes Muller who, in 1838, utilized it "to designate the cauliflower-like masses of connective tissue which fill a cystic cavity in the breast."[1] In 1941 Owens and Adams[2] listed thirty different names for the same lesion, and agreed with other authors that a more appropriate term was giant intracanalicular fibroadenoma of the breast.

Confusion regarding the exact nature of the lesion still exists, principally in relation to actual or potential malignancy; i. e. whether it is basically sarcomatous or benign. Although cases reported have emphasized that the lesion is benign in a vast majority of instances, ultimately lethal sarcoma has been noted also. In 1950 Steckler and Landman[3] found in the literature 3 reported cases of cystosarcoma phyllodes with metastases and described a fourth of their own. Saltzstein and Pollack[4] stated in 1949 that, in a review of 52 cases of cystosarcoma phyllodes, Pollack found 8 to be cancerous. McDonald and Harrington[5] protested the use of the term cystosarcoma phyllodes, believing that 90 per cent of the lesions so termed are benign and the other 10 per cent are fibrosarcoma. They agree with and quote Deaver's statement that "Large tumors of intracanalicular myxomatous type are not sarcomas and the term cystosarcoma should be abandoned."[5]

The following case report illustrates the accepted clinical and pathologic characteristics of cystosarcoma phyllodes with areas of fibrosarcoma in the stroma.

Case Report

Three years prior to examination the patient, a nulliparous white woman of 53, first noted itching and light "shock-like" pains in the left breast and a few weeks later discovered a small mass in the left breast. The mass exhibited only slight increase until 2 weeks prior to admission when there was sudden rapid development which continued

until the entire breast was involved by a mildly painful, draining lesion the size of a grapefruit (fig. 1).

Examination disclosed a large, bosselated growth, the nodular protuberances varying in diameter from 5.0 cm. to 2.0 cm. The overlying skin was red and small superficial ulcers which drained pink fluid surmounted the tumor. The breast was not tender and was freely movable over the chest wall. No axillary or supraclavicular adenopathy was palpable.

The remainder of the examination, including routine laboratory studies and chest x-ray, was within normal limits.

A provisional diagnosis of cystosarcoma phyllodes was made and a simple mastectomy was performed under general anesthesia with removal of the breast and the external pectoral fascia, but not the pectoral muscles. A large skin defect remained which was successfully covered with a split-thickness skin graft.

Postoperative examination at the end of 10 months failed to reveal evidence of local recurrence or adenopathy in the supraclavicular and axillary zones.

Pathology

Gross Examination: (Fig. 2) The specimen consisted of a cone-shaped breast 11.0 cm. across the base and 12.0 cm. in height, weighing approximately 800 Gm. There was normal appearing skin around the base, but at the apex

FIG. 1. Greatly enlarged left breast with marked skin changes including ulceration.

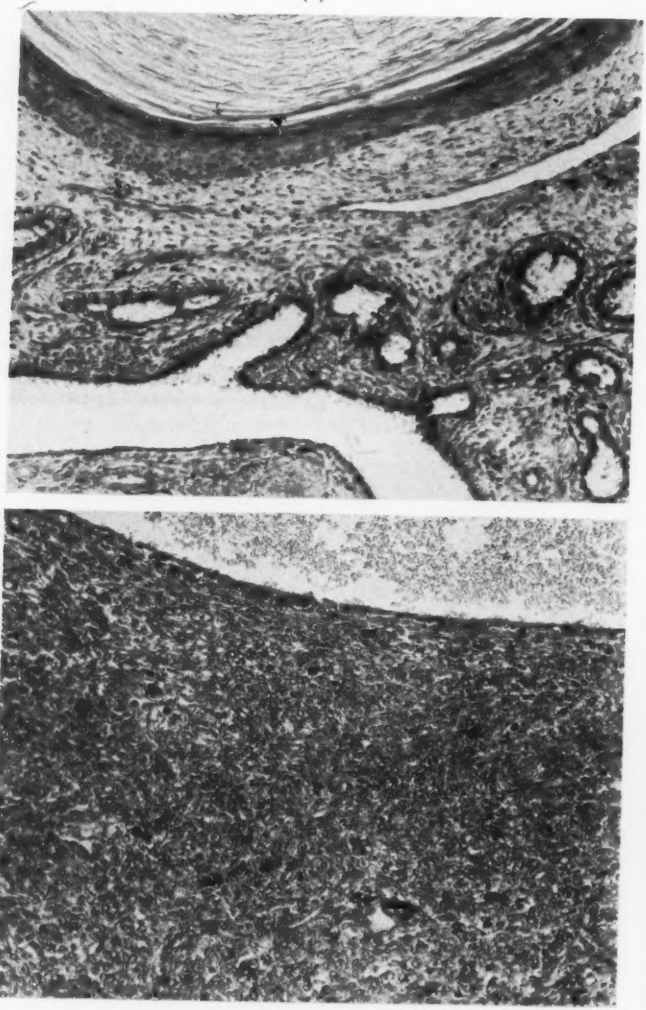
FIG. 2. Sectioned surfaces of gross specimen showing lobulated large tumor mass with bulging surfaces, partly smooth, homogeneous, and in part cystic. Neoplasm comprises major portion of specimen.

of the cone the skin was thinned, erythematous and glistening, and the surface nodular; these protuberances measured 5.0 x 3.0 cm. for the largest and 2.0 cm. for the smallest. Near the apex of the specimen the skin was ulcerated in several places and through these areas bulged red and pink friable tissue. The nipple was present near one of these ulcerated zones. Palpation of the external surface gave the impression of multiple nodules of firm tissue within the breast substance and not attached to the skin. On section, the specimen was found to be composed almost entirely of a coarsely lobulated fleshy tumor mass having irregular areas variably firm, soft, hemorrhagic and of necrotic appearance. There were numerous cystic structures present, containing opaque, gray-white material and averaging 1 cm. in diameter. The mass was demarcated from surrounding breast and fatty tissue, but there was no capsule. Muscle tags and fascia separated it from the deep line of excision.

Microscopic Examination: (Fig. 3) The neoplasm was formed by abundant connective tissue stroma and epithelial-lined spaces, at times irregular due to finger-like projections of stroma covered with epithelium. The epithelial cells for the most part appeared in several layers and were well-differentiated. In zones of fairly frequent occurrence circumscribed patches of squamous epithelium were observed, including keratinized masses. The stroma was of variable density, mostly loose and myxomatous, but with dense fibrous patches. In addition to these well-differentiated zones there were stromal areas of marked cellularity, cells round or spindle-shaped with frequent mitoses and occasional giant nuclear forms. The margins of the neoplasm were well-separated from the adjoining tissue. The zones of ulceration presented partly necrotic and myxomatous tissue projecting through the skin defect. Breast tissue outside the large mass was not unusual.

Pathologic diagnosis: cystosarcoma phyllodes, in part fibrosarcoma, of breast (left); squamous metaplasia, ulceration.

(a)



(b)

FIG. 3. (a) Microscopic section illustrating benign area with characteristics of fibroadenoma and with zones of squamous metaplasia (x70). (b) Microscopic section showing malignant area characterized by increased cellularity of stromal zone adjoining cyst. Many tumor giant cells and mitoses were present (x100).

Discussion

In 1931 Lee and Pack,[6] in a comprehensive survey of their own cases and 107 cases from the literature, concluded that the lesion developed from pre-existing intracanalicular fibroadenoma at a time of gelatinous metamorphosis of the stroma. As a rule a small mass had been known to exist for a number of years with little if any growth before a sudden acceleration to great size occurred; the average weight in their series was 7.6 pounds. Grossly the tumor was lobulated with variable areas of resistance and fluctuation and seemed to be encapsulated without invasion of the breast tissue. There was mobility and nonadherence to the skin or fascia. On section intracystic polypoid excrescences were observed separating fluid containing clefts. The stroma was myxomatous with cellular pseudosarcomatous zones. Lee and Pack were of the opinion that wide excision constituted successful treatment. In 91 cases discussed there were 6 recurrences.

In regard to history and gross appearance the lesion reported herein coincides with the cases described by Lee and Pack as giant intracanalicular fibroadenoma of the breast and as cystosarcoma phyllodes mammae by Johannes Muller. The presence of focal fibrosarcoma in the stroma places it as a malignant variant.

Unfortunately the term cystosarcoma phyllodes has a connotation of malignancy although the neoplasm, according to reported cases, is most often benign. It is not always possible, however, to discard a long-recognized term and it has been retained in this report. To prevent misunderstanding it seems necessary to qualify this basic diagnosis in order to indicate whether the tumor is benign or malignant. Since both epithelial and connective tissue elements are present, it is also important to designate the type of malignancy. Thus, in this case report we have chosen the complete diagnosis of cystosarcoma phyllodes, in part fibrosarcoma. Where no apparent malignancy exists the most logical diagnostic term would appear to be cystosarcoma phyllodes, fibroadenoma type, benign.

Because of the presence of sarcomatous change the advisability of further and more radical surgical therapy might be proposed. We concur in the opinion of Geschickter who has stated, "Since intracanalicular myxomas of giant size do not, as a rule, metastasize to the regional lymph nodes, whether or not the stroma shows the histologic features of sarcoma, amputation of the breast including the pectoral fascia and without axillary dissection is the treatment of choice."[7] However our patient is being followed for evidence of recurrence since this has been recorded in a small percentage of patients.

Summary

1. A case of cystosarcoma phyllodes, in part fibrosarcoma, is presented to exemplify the clinical characteristics and the accepted treatment of the disease.

2. The gross and microscopic appearance of the lesion is illustrated.

3. Although this lesion is generally benign, malignant variants have been

reported. Clarity in diagnosis requires that the term cystosarcoma phyllodes be modified to indicate the presence or absence of malignancy.

References

1. Ewing, J.: Neoplastic Diseases, a Textbook on Tumors. Philadelphia, W. B. Saunders Company, 1919, p. 4.
2. Owens, F. M., Jr. and Adams, W. E.: Giant intracanalicular fibro-adenoma of breast. Arch. Surg. **43**:558 (Oct.) 1941.
3. Steckler, C. and Landman, M.: Cystosarcoma phyllodes with metastasis. New York State J. M. **50**:339 (Feb. 1) 1950.
4. Saltzstein, H. C. and Pollack, R. S.: Benign tumors of breast. J.A.M.A. **140**:997 (July 23) 1949.
5. McDonald, J. R. and Harrington, S. W.: Giant fibro-adenoma of the breast, cystosarcoma phyllodes. Ann. Surg. **131**:243 (Feb.) 1950.
6. Lee, B. J. and Pack, G. T.: Giant intracanalicular fibro-adeno-myxoma of breast. So-called cystosarcoma phyllodes mammae of Johannes Muller. Am. J. Cancer **15**:2583 (Oct.) 1931.
7. Geschickter, C. F.: Diseases of the Breast, ed. 2. Philadelphia, J. B. Lippincott Company, 1947, p. 323.

ACUTE PORPHYRIA

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PORPHYRIA is a metabolic disease characterized by excessive excretion of porphyrins in the urine and feces. Clinically it appears to occur in two forms, congenital and acute. Congenital porphyria is rare and is distinguished by red discoloration of the teeth and bones and by photosensitivity of the skin. The acute form is much more common. It is actually a chronic disease characterized by remissions and exacerbations, with symptoms involving principally the nervous and gastrointestinal systems. Both forms are thought to be hereditary, the congenital being transmitted as mendelian recessive and the acute as mendelian dominant.[1] The following patient represents a case of acute porphyria.

Case Report

A 26-year-old housewife entered the Clinic complaining of "bad nerves." She had felt well until 4 weeks before admission when she developed "grippe" with chilly sensations, myalgias, transient diarrhea, and generalized crampy abdominal pain. The chilly sensations and diarrhea disappeared after 1 or 2 days. No fever was present. The patient continued to experience intermittent crampy abdominal pain, became constipated and required the use of repeated laxatives and enemas. She lost her appetite and vomited occasionally. There was a loss of 31 pounds during this period. In addition she had two attacks characterized by weeping, hyperventilation, carpal spasm, and inability to speak clearly; each lasted about 10 minutes. No loss of consciousness or sphincter control accompanied these episodes. As a result the patient became depressed and apprehensive. She was observed in a local hospital for 2 weeks, and was given barbiturates repeatedly for sedation. Her symptoms were ascribed to "nerves."

Family history revealed no similar illness. Her past history disclosed that she had experienced approximately six similar mild attacks of generalized abdominal pain beginning about the age of 15; each had lasted only a few hours. In 1947, during the second trimester of pregnancy, she underwent a similar attack accompanied by nausea and vomiting lasting 3 or 4 days. Her difficulty was diagnosed as acute appendicitis and she underwent an appendectomy, the pathologic findings of which are not known. There were no postoperative complications; however, 11 days later she had a recurrence of pain which lasted 3 weeks but subsided without further treatment. The patient subsequently delivered a healthy full-term baby after which she felt well until the onset of the present illness. Further questioning revealed that she had first noted dark brown discoloration of urine, coincident with the attack of "grippe" and this persisted until the time of admission to the Clinic.

Physical examination showed normal temperature and blood pressure. The pulse was 120 and respirations 24 per minute. The skin was sallow. There was no discoloration of the teeth. Slight generalized muscle tenderness was apparent and the abdominal

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reflexes were absent; the right Babinski reflex was equivocal; bilateral nystagmus on lateral gaze was evident on one occasion. The abdomen was soft and no masses were palpable.

Laboratory studies included normal blood counts and negative blood serology. Cephalin flocculation, thymol turbidity, and Tiselius protein fractionation were within normal limits. The fasting blood sugar was 92 mg. per cent, and a glucose tolerance test exhibited slight elevation at 30 and 60 minutes. Urinalysis showed a trace of albumin, and the urinary sediment contained occasional erythrocytes and 4 to 8 white blood cells per high power field. Freshly voided urine varied in color from amber to light brown, and turned dark brown on standing. Schwartz-Watson tests for urine porphobilinogen were repeatedly positive. Chest and skull x-rays showed no abnormality. An electroencephalogram was reported as "borderline with no evidence of epilepsy nor of focal cortical lesion." Proctoscopic examination and barium enema were negative. Exposure of the skin to ultraviolet radiation revealed no sensitivity. Neuropsychiatric examination suggested an anxiety hysteria reaction.

The patient was hospitalized for 11 days. She remained afebrile and manifested a slow fall in pulse and respiration to near-normal limits. Cramping abdominal pain was relieved by prostigmine bromide. One episode of visual hallucinations subsided spontaneously. She was discharged symptomatically improved. However, her local physician reported that she died several weeks later from ascending paralysis which affected first the legs and then the arms. No autopsy was performed.

Discussion

Acute porphyria is said to occur predominantly in women, usually in the third or fourth decades. Photosensitivity is rare. Pigmentation of the teeth does not occur although the skin may show diffuse pigmentation. Dark brown or red discoloration of the urine may appear intermittently, usually coincident with clinical activity of the disease. This discoloration may increase with standing or exposure to sunlight. Symptoms involve principally the nervous system and gastrointestinal tract.[1,2,3]

Gastrointestinal symptoms commonly include generalized crampy abdominal pain, nausea, vomiting, and severe constipation. Abdominal tenderness is poorly localized, and rigidity is slight or absent. The clinical picture may suggest an "acute abdomen" consistent with acute appendicitis, cholecystitis, pancreatitis, or intestinal obstruction. Many of these patients have been subjected to unnecessary and dangerous surgical procedures. The importance of considering acute porphyria in the differential diagnosis of the "acute abdomen" has been recently re-emphasized.[4]

Neurologic manifestations are variable in severity and character.[5,6] There may be involvement of both cranial and peripheral nerves. Weakness or paralysis of the extremities and the facial muscles is fairly common; ascending paralysis has been reported in a number of cases. Sensory changes are less common, but pain, paresthesias, and anesthesia have been recorded. Mental disturbances are observed frequently, and vary from irritability and hysteria to toxic psychosis with delusions and hallucinations. Convulsions may occur. The combination of mental symptoms with atypical neurologic and abdominal signs is often strongly suggestive of psychoneurosis, an impression inferred

by several observers in the case presented. Roth[5] has emphasized the frequent absence of knee jerks with intact ankle jerks, and the summation phenomenon in which tendon reflexes become increasingly active with continued tapping.

In 1941 Watson and Schwartz suggested a simple test to identify porphobilinogen—a substance which is excreted in the urine in acute (not congenital) porphyria.[7] Porphobilinogen, in the presence of Ehrlich's reagent and sodium acetate, is converted into an aldehyde insoluble in chloroform. It is readily distinguished from urobilinogen, which is completely extracted into the chloroform layer (figure). Subsequent studies have revealed that false positives are extremely rare, and the test is considered reliable in the diagnosis of acute porphyria.[8]

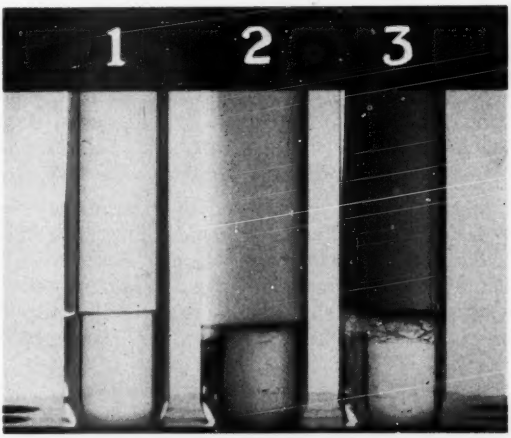

FIGURE. Watson test for porphobilinogen. Tube 1 is negative. Tube 2 is positive for urobilinogen (chloroform layer). Tube 3 is positive for porphobilinogen (water layer).

There is no specific treatment for the disease. Certain drugs have been reported as having initiated attacks in some instances and should, therefore, be avoided. These include barbiturates, sulfonamides, lead, alcohol, acetanilid, nitrobenzol, salvarsan, and trional. Prostigmine, which has been suggested for relief of abdominal cramps, seemed to be helpful in this patient.

Summary

A case of acute porphyria has been reported. It illustrates some of the commonly reported clinical and laboratory findings in this metabolic disorder. Porphyria should be considered in the differential diagnosis of cases presenting obscure abdominal and neurologic findings.

References

1. Nesbitt, S.: Acute porphyria. J.A.M.A. **124**:286 (Jan. 29) 1944.
2. Hayman, J. M., Jr.: Porphyria. Ohio State M. J. **45**:800 (Aug.) 1949.

3. Prunty, F. T. G.: Acute porphyria; investigations on pathology of porphyrins and identification of excretion of uroporphyrin I. Arch. Int. Med. **77**:623 (June) 1946.

4. Calvy, G. L.: Porphyria; a consideration in surgical diagnosis. Surg., Gynec. and Obst. **90**:716 (June) 1950.

5. Roth, N.: Neuropsychiatric aspects of porphyria. Psychosom. Med. **7**:291 (Sept.) 1945.

6. Schneck, J. M.: Porphyria; neuropsychiatric aspects in case of Negro. J. Nerv. and Ment. Dis. **104**:432 (Oct.) 1946.

7. Watson, C. J. and Schwartz, S.: Simple test for urinary porphobilinogen. Proc. Soc. Exper. Biol. and Med. **47**:393 (June) 1941.

8. Hammond, R. L. and Welcker, M. L.: Porphobilinogen tests on 1,000 miscellaneous patients in search for false positive reactions. J. Lab. and Clin. Med. **33**:1254 (Oct.) 1948.

DIODRAST ARTHROGRAPHY OF THE KNEE

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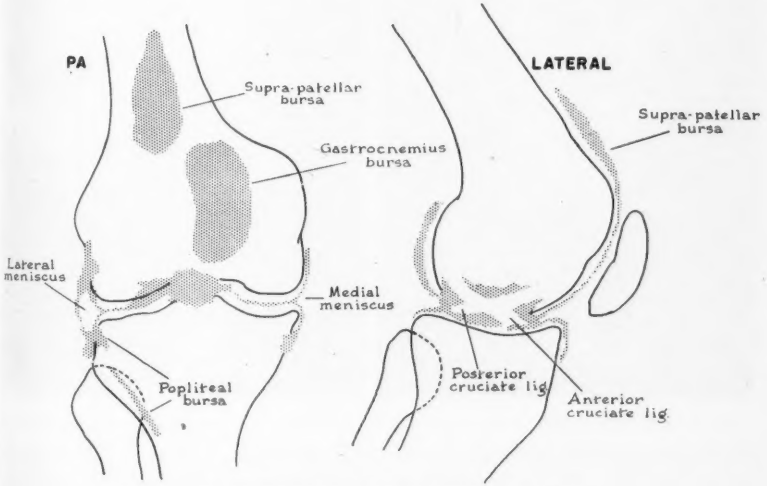
DURING the past 20 years contrast arthrography of the knee has enjoyed varying degrees of popularity. For the most part the contrast medium employed has been air or oxygen. Enthusiasm has been discouraged in this type of examination because of the actual technical difficulty of obtaining adequate contrast by means of gas. In our experience poor contrast and poor filling have made accurate diagnosis practically impossible. As a result we had discarded contrast arthrography until recent months. Its revival was based on the valuable work of Lindblom,[1] who has carried out some 6000 arthrograms employing parabrodil (diodrast) as the contrast media.

This article constitutes a preliminary report of our first 22 consecutive examinations of this type. To date the results have been good. The sharp contrast obtained with 35 per cent diodrast makes even the minimal pathologic change within the realm of accurate preoperative diagnosis (fig. 1a, b and c). This is partially explained on the ability of the iodine salt solution to mix with the synovial fluid and be imbibed on the cartilage and ligament surfaces. Sec-



DIAGRAMS OF DIODRAST ARTHROGRAMS OF KNEE

FIG. 1. (a, b and c) Normal posteroanterior, 45 degree oblique, and lateral views of diodrast arthrogram of knee. (d) Normal appearance of arthrogram one-half hour after injection of diodrast showing rate of absorption of opaque media.

FIG. 2. Diodrast in infrapatellar fat pad due to error in injection.

tions of the synovia at surgery showed no microscopic evidence of reaction to the contrast media. The procedure is simple and requires no special equipment.

A number 20 needle is inserted into the knee joint from the lateral side, angling beneath the patella. Any synovial fluid present is aspirated and 10 cc. of 35 per cent diodrast is injected. The knee is then manipulated to spread the media over the joint surfaces. Compression is applied on the anterior medial and the anterior lateral aspect of the suprapatellar area by means of pads held in place by an ace bandage. This forces the diodrast from the suprapatellar bursa into the joint space for better contrast. Anteroposterior, posteroanterior, lateral, and 45 degrees oblique stereoscopic films are then exposed. The stereoscopic shift is 6 degrees and is of great importance in the proper localization of small collections of opaque media at the menisci. A routine film is made one-half hour after the injection for evaluation of the absorption ability of the synovial membrane. Normally only a trace of diodrast remains at this time (fig. 1d). No technical difficulties were encountered in the procedure except on one occasion when the opaque media was injected into the infrapatellar fat pad (fig. 2). There was no clinical reaction, however, and the diodrast was rapidly absorbed. Almost all patients we have examined were referred from the Department of Orthopedics and represented cases of old and new trauma involving cartilage and ligaments. As a result our pathologic findings consist of tears of the medial and lateral menisci, ruptures of the anterior cruciate ligament,

FIG. 3. (a and b) Diodrast arthrograms showing a tear in medial and lateral meniscus respectively as indicated by arrows. (c) Tear in medial meniscus as occasionally demonstrated by filling defect and associated aberrant bursa. (d) Postoperative arthrogram showing absence of medial meniscus.

CLINICAL	PLAIN FILMS	ARTHROGRAM	SURGERY
r anterior and posterior iciates r medial meniscus	Normal left knee	Tear lateral miniscus, posterior Tear anterior cruciate ligament	Tear lateral, miniscus Tear anterior cruciate
r med. men.	Normal right knee	Normal	No
r med. men.	Normal right knee	Tear med., men., post.	Tear med. men., post.
r med. men., post.	Normal right knee	Normal	No
r med. men.	Narrowing med. joint space with minimal arthritic changes; left knee	Tear med. men., ant.	Tear med. men., ant.
pical absence of med. men. idual internal derangement ovitis	Slight narrowing med. joint space; left knee	Absent med. men. ? Tear lat. men., lat. and post. Baker's cyst Deformity ant. cruciate Chronic synovitis	Absent med. men. Normal lat. men. Baker's cyst Chronic synovitis
d. men. injury ovial thickening; minimal	Min. osteoarthritis; left knee	Tear med. men., lat. and post.	Tear med. men.
t lat. men.	Normal right knee	Atypical changes, lat. men.	Tear lat. men.
er's cyst. Possibly a frag- nt of post. med. men. re- ining	Slight narrowing med. joint space	Small Baker's cyst; incomplete removal med. men.	No
r med. men.	Normal right knee	Tear lat. men., post.	No
r med. men.	Normal right knee	Tear lat. men., post.	No
r med. men.	Normal right knee	Tear med. men., lat. and post. Separation ant. portion of capsule from med. men.	Tear med. men.
r med. men., ant.	Normal right knee	Normal	No
r med. men.	Normal right knee	Tear med. men., lat.	No
ear lat. men. iscoid men. yst lat. men., post.	Normal left knee	Normal	No
r med. men.	Normal left knee	Incomplete filling about med. cartilage with atypical med. bursa indicative of med. men. lesion	Tear med. men., post. Atypical bursa adjacent to post. med. men.
r med. men.	Normal right knee	Tear med. men., lat. and post. Tear lat. med., lat.	No
r med. men.	Normal right knee	Large Baker's cyst	No
t lat. men.	Normal left knee	Normal	No
r med. men., post.	Normal left knee	Normal	No
r med. men.	Normal left knee	Tear med. men., post. Luxation of fragment of med. men. into inferior recess	No
ronic mild med. Collateral ment strain	Normal left knee	Normal	No

FIG. 4. Lateral diodrast arthrogram demonstrating large Baker's cyst.

and Baker's cysts (figs. 3, 4). Although in many cases the arthrogram was only confirmatory, in occasional instances the findings were remarkable and hitherto unsuspected (table).

Summary

Contrast arthrography with the use of 35 per cent diodrast is apparently a simple, safe, and accurate means of diagnosing pathologic changes of the knee joint induced by trauma. A further study is indicated to determine its usefulness in varying arthritic conditions.

Reference

1. Lindblom, K.: Arthrography of knee. Acta radiol. Supp. 74, p. 1-111, 1948.

ANNOUNCEMENTS

Certificate Ceremony and Award of Thesis Prize

On June 19 certificates were awarded to 14 Fellows who had completed their formal training in the following fields: Internal Medicine: R. V. Choisser, J. A. Ecker, J. Geiger, C. F. Kane, C. G. Suter, F. W. Watkins. Neurology: H. J. Tucker. Ophthalmology: C. B. Kitchen. Orthopedic Surgery: R. H. Lamb. Otolaryngology: C. C. Woodburn, Jr. Surgery: A. G. Michels, E. W. Rumsey, E. C. Sifers. Anesthesiology: C. E. Wasmuth.

At the same ceremony the 1951 Lower Fellowship Thesis Prize was presented to Dr. Cary G. Suter for his paper entitled *Anomic Aphasia*. This prize was established in 1935 by Dr. William E. Lower.

Appointments

Dr. John F. Whitman was made a member of the staff in the Department of Cardiovascular Diseases on July 1, 1951. Dr. Whitman graduated from the University of Michigan in 1940 and from Tulane University School of Medicine in 1945. He served an internship at the State of Wisconsin General Hospital, and a fellowship at the Cleveland Clinic from July 1946 to July 1949 at which time he became a member of the assistant staff. He has written articles for the *Cleveland Clinic Quarterly* among other contributions to the medical literature. Dr. Whitman belongs to the American Heart Association.

Dr. Willard Parker has been appointed to the staff in the Department of Otolaryngology effective August 1, 1951. Dr. Parker graduated from the University of Michigan in 1941 and from the University of Michigan Medical School in 1944. He interned at Wayne County General Hospital, Eloise, Michigan, and served his residency at the University of Michigan Hospital where he is now chief resident in Otolaryngology. Dr. Parker was in military service for 2 years.

Dr. Robin Anderson has been appointed to the staff in the Surgical Division to establish a new Department of Plastic Surgery. The appointment will be effective August 1. Dr. Anderson graduated from Princeton University in 1939 and from Harvard Medical School in 1943. He served as intern and assistant resident at Children's Hospital in Boston for 2 years and spent 2 years at Ohio State University. At the present time he is completing his second year with Dr. James Barrett Brown and his group at Barnes Hospital, St. Louis. Dr. Anderson served in the U. S. Army for 3 years during which time he specialized in plastic surgery, his principal professional interest. He has contributed articles to the medical literature.

The American College of Physicians met in St. Louis, Missouri, in April, 1951. Dr. H. R. Rossmiller organized a reunion of former Cleveland Clinic Fellows in Medicine at the New Jefferson Hotel, April 10. The get-together was most enjoyable and the committee hopes for similar reunions in conjunction with future meetings. While the exact record of attendance is not complete, the following list comprises the acceptances:

P. L. Byers, 5400 Norwood Road, Kansas City 3, Kan.; Woodrow M. Campion, Medical Arts Clinic, Liberal, Kan.; William G. Ensign, Northwest Clinic, Minot, N. D.; W. E. Flannery, 24 E. Grant St., New Castle, Pa.; John J. Grady, 15000 Madison Ave., Lakewood, O.; Lawrence J. Halpin, Merchants National Bank Bldg., Cedar Rapids, Iowa; Gordon M. Hankins, Employees' Hosp. Tenn. Coal, Iron and R. R. Company, Fairfield, Ala.; F. B. House, 326 N. Ingalls St., Ann Arbor, Mich.; Ralph E. Hibbs, 1032 W. Main, Medford, Ore.; R. H. Jacques, 118 E. Jeffry Place, Columbus 2, O.; T. Reid Jones, 1107 Bryant Bldg., Kansas City, Mo.; Leslie C. Kindschi, Monroe, Green County, Wis.; Thomas H. Lambert, Scripps Metabolic Clinic, LaJolla, Cal.; William B. Leffler, 341 Mt. Vernon Ave., Marion, O.; W. F. Owen, Jr., 526 W. 17th St., Santa Ana, Cal.; Clark P. Pritchett, 463 E. Town St., Columbus, O.; John Rumsey, 2001 Fourth Ave., San Deigo 1, Cal.; Maurice Snyder, 105 S. Seventh St., Salina, Kan.; Cleo W. Stevenson, 1469 Poplar Ave., Memphis 4, Tenn.; Ross V. Taylor, 290 Michigan Ave. W., Jackson, Mich.; Walter R. Tupper, 119 N. Central Ave., Glendale, Cal.; Lee C. Underwood, Peoples Bank Bldg., Canton 2, O.; George J. Ward, 15 Dwight St., Poughkeepsie, N. Y.; R. M. Watkins, 10515 Carnegie Ave., Cleveland 6, O.; Allen N. Wiseley, The Western Montana Clinic, Owen and West Broadway, Missoula, Mont.; C. P. Wofford, 200 E. Main St., Johnson City, Tenn.

A Postgraduate Course on "The Diagnosis and Treatment of Cardiovascular Disease" will be given at the Clinic under the auspices of the American College of Physicians from October 22 to October 27. The Course will place emphasis on current concepts of pathologic physiology and recent advances in the diagnosis and treatment of cardiovascular disease. The major forms of cardiac and peripheral vascular disease and their complications will be considered in detail, and there will be discussions also of less frequently encountered conditions. Newer knowledge in electrocardiography and roentgenologic diagnosis will be reviewed, and the surgical treatment of heart disease will be covered in several presentations. The Course will include lectures, clinical demonstrations, and question and answer panels.

Application should be made to Mr. E. R. Loveland, Executive Secretary, The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.